Peripheral Circulation

in health and disease

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PART V THE ANATOMIC BASIS OF THE PERIPHERAL CIRCULATION IN MAN

Preface

The recrudescence of interest in the treatment of peripheral vascular disease engendered by the development of a large number of synthetic drugs makes the present volume most timely. It is thoroughly up to date and because it is so comprehensive, covering all the main aspects of peripheral vascular disease, it should, I believe, not only be useful to medical students in general and particularly to workers directly concerned with this field, but it should also prove invaluable to practitioners of general medicine.

The first part of the book deals thoroughly with the pertinent anatomy and physiology of the vascular system, together with a detailed description of both the very simple clinical tests of the circulation and the more complicated laboratory procedures. The second part gives an unusually well organized description of the pathologic alterations that can occur as well as a rather complete enumeration of the resulting disease entities of the peripheral circulation, both arterial and venous. The third part sets forth the physiologic vascular adjustments which arise in response to the various pathologic states, while the fourth section presents an up to date summary of the available means of management of arterial and venous disease, both medical and surgical. This well planned arrangement will thus provide easy access for both students and practitioners to the particular points in which they are interested.

The special fifth section should prove especially rewarding to medical students and investigators interested in basic science aspects of this field, as should the extensive bibliographies that appear throughout the volume and form an integral part of it.

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Introduction

THE INCREASING INTEREST in diseases of peripheral blood vessels and the likewise increasing tendency to provide a sound physiologic basis for their proper evaluation and management have led to a large volume of new investigative work in this field the development of new methods of investigation and the application of these methods to clinical medicine Such fruitful though widely scattered studies call for a re evaluation of the problems facing the student of peripheral circulation and the disease states stemming from its disturbances

This book is an attempt at such re evaluation Consequently pathologic manifestations have been correlated wherever possible with disturbances of specific physiologic mechanisms less emphasis has been placed on rigidly labeled classifications of the peripheral vascular diseases Many workers in the field believe that all too frequently such detailed classifications are not supported by sufficient pathologic and histologic evidence

Moreover knowledge of the basic anatomy of large and important parts of the vascular tree has been far from complete The recent work of Dr Saunders and his co workers on the anatomy of the blood channels supplying human skeletal muscles and on the peculiar functional distribution of these channels within the musculature fill in some of the gaps in our knowledge Dr Saunders findings have been incorporated in this book as a special and separate section because they represent at present the most accurate demonstration of the fact that physiologic deductions can be based on structural information only if such information is complete This necessity for basic facts of course applies to pathologic conditions as well or even more

It is necessary to realize that changes and disturbances in peripheral blood flow are not necessarily associated with demonstrable structural changes and, even more important can not always be easily correlated with such By now it is common knowledge that morphologic findings even if secured through biopsy do not necessarily reflect functional changes in an organ Moreover observed structural changes may be compatible with intact physiologic functions and disturbed function may be found in the absence of any demonstrable structural changes This of course does not mean that a structural classification should or can be entirely disposed of It remains a necessity for didactic purposes however such a classification should be supplemented with and supported by correlation of disease manifestations with demonstrable changes in physiologic function

Except for Dr Saunders section illustrations have been limited to such anatomic and physiologic charts and diagrams as appear indispensable for better understanding of the basic mechanisms of peripheral blood flow Illustrations of apparatus as well as of clinical manifestations of vascular disease have been omitted

Part I Basic Aspects of Peripheral Blood Flow

Chapter 1 Anatomy and Physiology of the Vascular System

THE VASCULAR TREE AND ITS INNERVATION

A LENGTHY DESCRIPTION of the entire vascular system is obviously beyond the scope of this book such information is readily obtainable from any standard text on anatomy However a better understanding of the subject requires at least a sketchy review of the vascular tree with emphasis to a greater or lesser degree on such of its branches as are concerned with the circulation in the extremities [1]

1 Blood Supply of the Upper Extremity The primary arterial channel to the upper extremity is the axillary artery which is the direct continuation of the subclavian branch of the aorta After giving off its branches to the muscles in the shoulder girdle and the upper arm and those that form the anastomoses with the branches from other arteries in the chest at the lower end of the axilla it continues directly into the brachial artery Accompanied by two brachial veins and the median nerve the brachial artery passes downward beneath the brachial fascia in the medial bicipital groove to the cubital fossa where it lies upon the tendon of insertion of the brachialis muscle covered by the lacertus fibrosus Its branches supply all the muscles of the arm and the humerus It also gives off the superior and inferior ulnar

arteries which supply neighboring muscles and terminate by forming the cubital articular rete At the bend of the elbow the brachial artery divides into two terminal branches the radial and ulnar arteries At first the radial artery runs between the lacertus fibrosus and the tendon of the biceps it then passes to the ulnar side of the superficial radial nerve under cover of the brachio radialis and runs downward in the groove between this and the forearm flexors first in front of the tendon of the pronator teres and then between the brachioradialis and the flexor carpi radialis It rests for some distance on the flexor pollicis longus and for a short distance on the pronator quadratus and in the lower third of the forearm it is covered only by the antebrachial fascia and lies accordingly quite superficially in front of the styloid process of the radius Below this it bends under the tendons of the abductor pollicis brevis to the dorsum of the hand, traversing the radial faveola and there passing between the two heads of the first dorsal interosseous muscle to the volar surface of the hand to form the deep volar arch

The ulnar artery the other and larger terminal branch of the brachial artery curves gradually toward the ulnar side of the volar surface of the forearm being situated on the origin of the flexor digitorum profundus and behind the median nerve and the superficial flexors It comes to lie on the radial side of the ulnar nerve remains covered by the flexor digitorum sublimis and flexor carpi ulnaris until the lower fourth of the forearm where it lies between the tendons of these two muscles close beside the ulnar nerve With this it runs over the radial surface of the pisiform bone between the volar and the transverse carpal ligament and so covered at first by the palmaris brevis to the palm of the hand where it becomes the chief constituent of the superficial volar arch

Branches from the radial and ulnar arteries supply the muscles of the forearm the radius ulna and carpal bone and their finer ramifications from various retia around the elbow and about the wrist joint

The blood supply of the hand and fingers is derived principally from the branches of the superficial and the deep volar arches which are formed by the anastomosis of the terminal branch of the ulnar artery with the superficial volar branch of the radial and of the terminal branch of the radial artery with the deep volar branch of the ulnar respectively The common volar digital arteries from which the proper digital arteries arise and the volar metacarpal arteries are derived from these arterial arches

After further subdividing into branches of increasingly smaller caliber they ultimately form the arterioles beyond which the muscularis is lost and the vascular tree consists of endothelial tubes the capillaries its smallest unit Through the capillary wall gaseous and metabolic exchange with the tissues takes place Through the capillary beds blood is carried into the finest units of the venous portion of the circulation These vessels in turn join one another forming channels of increasing sizes

Vascular drainage of the upper extremity is accomplished through a superficial and a deep set of veins The cephalic vein starts at the radial side of the dorsum of the hand from the dorsal venous network and the digital venous arches It receives tributaries from the volar surface of the hand the intercapitular vein and passes up the radial side of the forearm as far as the bend of the elbow where it anastomoses with the basilic vein It passes up the upper arm as a rule somewhat smaller than it is in the forearm in the lateral bicipital groove to the deltoidespectoral triangle where it pierces the fascia to open into the axillary vein The basilic vein arises on the ulnar side of the dorsum of the hand It runs upward on the ulnar side of the volar surface of the forearm to the level of the bend of the elbow where it unites obliquely by means of the median cubital vein with the cephalic It continues upward in the upper arm in the medial bicipital groove and at about the middle of the arm pierces the brachial fascia and opens into the medial brachial

vein which i usually its direct continuation

The deep veins of the upper extremity accompany the arteries a paired venae comites They take origin in the deep and uperficial volar venous arches and terminate with the brachial vein from which the axillary vein i formed They are connected by numerou ana tomoses with the uperficial veins and during their course along with the arteries the members of each pair are frequently connected by tran verse ana tomoses

The axillary vein runs through the axilla medial to and in front of the axillary artery to open into the ubclavian vein which in turn drains into the innominate vein The right and left innominate veins unite to form the uperior vena cava

2 Blood Supply of the Lower Extremity At about the level and in front of the body of the 4th and 5th lumbar vertebrae the abdominal aorta bifurcates to form the two common iliac arteries which run for 5-6 cm along the medial border of the p oas muscle crossed by the ureters and divide into their two terminal branches the external and internal iliac arteries without giving off any other branches of even moderate ize The internal iliac (hypoga tric) artery upplies primarily the pelvic vi cera the perineum and the mu cle of the pelvic girdle The external iliac artery terminates on the border of the poa mu cle beneath the inguinal (Pou part s) *ligament*, where it pa es directly into the femoral artery after giving off ome branche to upply the lower abdomen the inguinal region and the pubi The femoral artery runs uperficially through the iliopectineal fo a and the femoral trigone covered by the fa cia lata at fir t lateral to and then in front of the femoral vein and medial to the femoral nerve It then enters the adductor canal covered by the artorius muscle and pa es through the adductor hiatu into the popliteal fos a *to become the popliteal artery* It gives off mu cular branches to the mu cles of the hip and thigh nutrient branches to the femur branches to the kin of the lower abdomen and of the pubi to the external genitalia as well as branches to the gluteal ana tomoses and the arterial retia about the knee joint and the femoral trochanter

The popliteal artery begins at the adductor hiatu and run through the middle of the popliteal fo a re ting on the femur and the posterior urface of the knee joint and somewhat medial to the vein pa es between the two heads of the ga trocnemiu muscle over the posterior urface of the popliteu mu cle and under the popliteal arch of the oleu and in the popliteal canal divide into its two terminal branches the anterior and posterior tibial arteries It branches upply the ti ues in the lower thigh, knee and upper leg and contribute largely to the ana tomo es around the joint

The po terior tibial artery pa es downward with the tibial nerve between the oleus and the deep flexors and in the lower third of the leg emerge from under the medial border of the oleu and comes to lie beneath the fa cia It then runs behind the medial malleolus under the laciniate ligament to the sole of the foot where it divides into its terminal branches the medial and lateral plantar arteries the latter joining with the deep plantar branch of the dor al pedal artery to form the plantar arch It gives off nutrient branches to the tibia fibula and the tar al bones branches to the oft ti ues of the leg and ankle as well as ana tomotic branches to the region of the knee the lateral and medial malleoli and the calcaneal retia

The anterior tibial artery which upplies ju t about the ame tructures a the posterior tibial artery pa es between the tibia and fibula and runs downward on the anterior urface of the intero seou membrane It lies at fir t between the tibialis anterior and the exten or halluci longu accompanying the deep peroneal nerve It pa es under the cruciate ligament resting on the bone and the cap ule *of the ankle joint when it reaches the dor* um of the foot it becomes known a the dor al pedal artery which pa es upon the dor um of the foot between the tendon of the exten or hallucis longus and the exten or digi

torum longus and resting on the dorsal sur faces of the tarsal bones takes a straight cour e to the first metatar al space where it divides into its two terminal branches the first dorsal metatar al and the deep plantar artery

The foot and toes thus derive their blood supply from the plantar metatarsal and plan tar digital branches from the plantar arch the medial and lateral plantar arteries from the posterior tibial artery and the tar al dorsal metatarsal and dorsal digital branch of the dorsal pedal artery from the anterior tibial artery, which branches also from the dorsal pedal rete and contributes to the lateral and medial malleolar and calcaneal retia

The e arteries subdivide into increasingly smaller branches until they form the arterioles which in turn give off the capillaries The e minute vessels then unite with one another forming the initial portions of the venous sys tem Subsequent unions of the e ve sels form increasingly larger venous channels

As in the case of the upper extremities the venous drainage in the lower extremities may be divided into a superficial and deep set The great saphenous vein the large t super ficial vein in the body arises on the dorsum of the foot from the dorsal venous rete and from the medial end of the dorsal venous arch It receives some veins from the plantar re gion and then pa es up the medial urface of the lower leg and thigh inclining toward the anterior surface in the upper third of its cour e It pa e over the falciform border of the fa cia lata and empties into the femo ral vein On its way it receives numerous branche tho e of the thigh being the larger and just before its termination it receives the uperficial epiga tric and uperficial circum flex iliac veins and usually also the external pudendal The other large uperficial vein of the lower extremity is the mall saphenous vein which ari es on the lateral side of the dor um of the foot It a cends behind the lateral malleolus on the po terior urface of the lower leg and in the groove between the two heads of the ga trocnemius it pierces the fa cia to open into the popliteal vein in the popliteal fos a Before its termination it re ceives a vein from above the femoropopliteal and by this and other anastomoses is brought into connection with the great saphenous It is also connected with the deep veins of the lower leg by a strong branch

The deep set of veins has its origin from doubled anterior and posterior tibial veins that unite to form the popliteal vein which is double only in the lower part of its course The popliteal vein follows the course of the popliteal artery through the popliteal fossa lying behind and somewhat lateral to it to become the femoral vein In the lower part of its course in the adductor canal it lies be hind the artery but pa es medially as it as cends and in the region of the fossa ovalis and below the inguinal ligament it is medial to the artery It receives the deep femoral vein the great saphenous and usually a num ber of small branches corresponding to the branches of the femoral artery These last are double as is al o the deep femoral though this usually becomes single before its termi nation

In the lacuna vasorum the femoral vein continues directly to become the external iliac vein receiving two tributaries the inferior epigastric and the deep circumflex iliac and pa es upward medial to and behind the femo ral artery to form with the hypoga tric (in ternal iliac) vein the common iliac vein an terior to the acro iliac articulation The two common iliac vein are the principal parietal tributaries of the inferior vena cava

3 Histology and Innervation of the Vascular Tree The vessels constituting the vascular bed differ widely in their calibers in different regions and on the basis of their size structure and phy iological relationships are divisible into four main groups the ar teries arterioles capillaries and vein * The arteries eem constructed to with tand high pre sure Their wall are thick and contain a larger proportion of ela tic ti ue a maller proportion of involuntary mu cle fibers an outer sheath of connective tis ue and an inner

lining of endothelial cells the three coats from without inward are called the tunica adventitia media and intima The elements of the tunica adventitia gradually merge with those of the surrounding loose connective tissue which accompanies every blood vessel The relative proportions of muscular and elastic tissues vary with the size of the artery The wall of the largest arteries (e g the aorta) differ from the wall of arteries of medium caliber (e g the radial artery) by its absolute thickness and by its structure The middle layer of the largest vessels such as the aorta and the pulmonary artery are relatively poor in muscular tissue but contain a large proportion of elastic fibers The medium sized arteries contain a relatively large amount of muscle and less elastic tissue while in the smaller vessels the muscle is greatly in excess The walls of the arteries are supplied with minute vessels — the vasa vasorum — which ramify in the outer and middle coats The arterial walls are abundantly provided with nerves As the arterial system is traced peripherally the vessels are found to break up into innumerable branches whose calibers become reduced with successive divisions While the caliber of the arteries gradually decreases as they recede from the heart the sum of the diameters of the lumens of all the branches of these arteries increases greatly the further they are from the heart

The smallest arteries 0 3 mm in diameter or smaller are usually grouped in a separate class and are called arterioles These arterioles vary in size but on the average are about 0 2 mm in their outside diameter Their walls are relatively thick and are composed almost entirely of smooth muscle lined by an *endothelial* layer and sheathed by a scanty adventitia The muscle fibers are richly supplied with nerve fibers After a course of variable length the arterioles lose their muscular *and connective* tissue coats while the inner endothelial tube that remains are continued as extremely fine hairlike vessels — the *capillaries* In the transition between the arterioles and the capillaries some authors distinguish precapillary arterioles

The capillaries, several of which arise from a single arteriole are from 2 to 10 microns in diameter (in man average 8 microns) depending upon volume of blood flowing through them and from 0 5 mm to 1 0 mm long A network of reticular fibers forms a thin membranous sheath around the capillaries and separates them from the elements of the other tissues Usually capillaries are accompanied by fixed macrophages probably undifferentiated cells of mesenchymal origin and a few scattered nerve cells which can only be identified through the use of special histological methods In amphibians and certain other cold blooded vertebrates a scattering of peculiar cells with a number of long processes is seen lying upon the outer surface of the capillary wall These are called Rouget cells after their discoverer The processes of the neighboring Rouget cells join with one another to form a loose meshwork that encloses the capillary These cells have been seen to contract under electric stimulation They have been described by some workers on the walls of human capillaries [6] others have not been able to confirm this [8] The capillaries form mazelike plexuses with one another and connect the arterial and venous system

The capillaries arise from the *terminal* branches of arteries and drain into the beginning of the venous system they form exclusive networks by their frequent branchings and anastomoses These networks thoroughly penetrate the various tissues they nourish In most instances the meshes of the capillary network *adjusting themselves to the available* free spaces between the elements of the tissues have a polygonal shape and are of approximately equal size in all planes

The only component the capillary has in common with all other parts of the vascular tree including the heart is the endothelium Most workers actually believe that the whole capillary structure consists only of the endothelial tube Recently however Kisch has found with the electron microscope that this endothelial tube is much *more complicated a* structure than heretofore assumed [9]

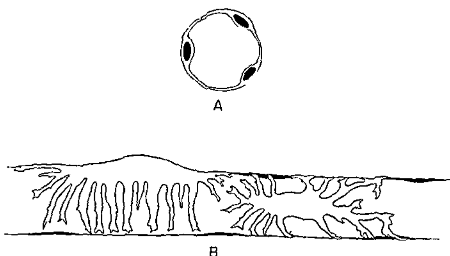


Fig 1

A Schematic drawing of cross section through a capillary Note depiction of the concept of a simple tube formed by a syncytium of endothelial cell

B Schematic drawing of longitudinal aspect of a capillary depicting Rouget Meyer cells adjacent to the tube with irregular excrescences of the cytoplasm (basket cell formation)

In the living animal it is usually possible to distinguish the endothelial nuclei scattered along the outlines of the capillaries After fixation and staining the wall of the capillaries stands out clearly as a thin homogenous membrane, within which the endothelial nuclei are located at various distances from one another

The caliber of the capillaries in various parts of the body varies within narrow limits related to the size of the red blood corpuscles In man it averages around 8 microns Patent thin capillaries through which only blood plasma circulates probably do not exist although great number of the capillaries are collapsed when the organ or tissue is resting When the organ begins to function actively these collapsed capillaries may open up and blood then circulates through them

Studies made on living blood vessels in chambers inserted in a rabbit ear indicate that capillary contractility in the mammal *does not depend on the Rouget cell* Microdissection studies have shown that the endothelial cell may contract after direct mechanical stimulation Capillary circulation has also been observed in the mesentery of the rabbit the wing of the bat and the web of the frog

Vonwiller[10] in man and Chambers and Zweifach[11, 1] in the animal have shown that changes in the diameter of the capillary lumen are dependent upon the state and shape of the endothelial cell rather than upon any contractile elements

The transition between arteries and capillaries and between capillaries and veins is gradual This applies to the structure of the wall as well as the caliber of the vessel However capillaries are often found which project directly from small arteries before a complete ramification of the latter has taken place similarly accessory capillaries frequently enter directly into a *well developed* small vein

It has also been shown that in addition to *the capillary networks above described there* may be seen arteriovenous anastomoses which connect an arteriole directly to the venous system without undergoing finer subdivisions It appears that physiologically they do not play an important role in gaseous and metabolic exchange but rather act as shunts that



FIG 1 C Electron microscopic photograph of cross section through a capillary (heart of guinea pig) Note (1) one single cell forms the capillary wall (2) the nucleus is distinctly seen the cytoplasm is of varying thickness and has protrusions of various shapes into the capillary lumen in which a red cell is seen (3) there is a distinct rather smooth outer membrane" and a distinct inner membrane" which varies in thickness *(The electron microscopic photographs shown in figs 1C D and E were taken by Dr Bruno Kisch Director of the Electron Microscope Laboratory of the American College of Cardiology the authors are deeply indebted to Dr Kisch and wish to express their thanks and appreciation)*

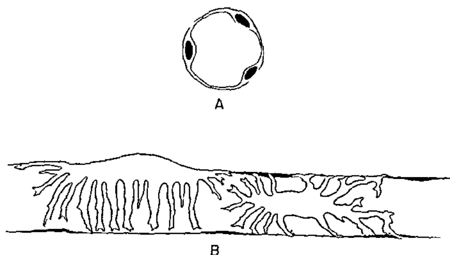


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FIG 1 E. Electron micro copic photograph of cro s section throu h a capillary (heart of guinea pig) In addition to the features described under C the triangular large nucleus of a Rouget Meyer cell is shown sitting on the capillary wall Filiform excre cences of the cytopla m virtually engulf the capillary



FIG 1 D Electron micro copic photograph of oblique section through a capillary (heart of guinea pig) *In addition to the features d cribed under C ti o nuclear cro s ections are een* which may repre ent either ti o nuclei or a single nucleu section d twice

ties the proximal innervation is supplied by postganglionic nerve fibers from the aortic plexus in the abdomen These fibers follow the common and external iliac arteries to the thigh and terminate at the proximal parts of the femoral artery The distal innervation to the smaller arteries arterioles and capillaries in the lower extremity is conveyed through postganglionic nerve fibers running through the nerves of the lumbo sacral plexus

The existence of vasodilator fibers in animal is well established In man however they have not been demonstrated but their existence is very strongly suggested by clinical and experimental evidence[1, 19] Vasodilator impulses emerge from the central nervous system at three levels The highest level is through the cranial outflow of the parasympathetic division of the autonomic nervous system where the impulses are conveyed through the chorda tympani the glosso pharyngeal and the vagus nerves The second level is through the thoracico lumbar outflow where the vasodilator fibers presumably pursue the same routes as the vasoconstrictor fibers The lowest level is through the sacral outflow where the fibers are conveyed through the pelvic nerve Antidromic vasodilator impulses are also conveyed through the posterior spinal nerve roots[20]

Aside from the vasomotor nerves other nerve fibers may be seen in the walls of the blood vessels These are medullated fibers and are afferent conveying sensory (pain) impulses *from the vessels as well as antidromic* (dilator) impulses

The appearance of the first smooth muscle cells or denser collagenous fibers in the vessel wall indicates the beginning of a small vein The concept of arterial and venous capillaries in man is rather indefinite and it is often impossible to distinguish them by the width of their apertures from ordinary capillaries[4]

Their venous ends converge to form first the smaller vein or venules By the confluence of these to form larger channels and the successive junctions of veins of ever increasing caliber the blood is finally poured into the right auricle by two large trunks the superior and inferior venae cavae The veins have much thinner walls than the arteries but like these they possess three coats intima media and adventitia The middle coat is only a fraction of the thickness of that of a corresponding artery It is composed of a relatively small amount of unstriped muscle and a large amount of connective tissue the elastic tissue is scanty The outer coat of the vessel is disproportionately thick being several times thicker than the tunica media The valves present in some of the larger veins are formed by foldings of the tunica intima

THE CONCEPT OF VASOMOTION

The most basic physiologic characteristic of any organ or structure within the living animal organism is its particular type of response to stimuli Blood vessels in general respond by changing their (circular) lumen the lumen becomes either narrower or wider The physiologic process of change of lumen in blood vessels is called vasomotion Whenever the direction of vasomotion is toward narrowing of the lumen the term vasoconstriction is used whenever vasomotion tends to widen the vessel lumen the term vasodilation is used The end result in the latter case is mostly referred to as vasodilatation This terminology has been used rather glibly and has been accepted too uncritically It is necessary to define more clearly the structural *substrates of these physiologic events*

The differences in structure of the various segments of the arterial tree—the relative proportion of muscular and elastic tissues varying with the size of the artery (more elastic tissue in the larger and more muscle in the smaller)—indicate differences in function and physiologic behavior within the arterial system itself

It may be justifiably assumed from direct observation as well as from functional tests that blood vessels of arterial nature that are characterized by the possession of a clearly discernible muscular coat can narrow

can allow the blood to pass through the part with lesser or greater rapidity which at times may even cause the total short circuiting of the circulation *to the exclusion of other parts* of the organ or tissue[13] A third, and seemingly intermediate type of capillary is seen especially in the skin At the bases of the dermal papillae, *the arterioles are seen to give* off endothelial tubes which ascend into the papillae and turning upon themselves join neighboring loops to form collecting venules *These capillary loops are easily demonstrable* at the base of the fingernail where they are seen arranged in horizontal rows of hairpin shaped vascular structures[14] Each capillary loop *consists of an ascending afferent* (arterial) limb an arch or transition piece and a descending efferent (venous) limb In tracapillary pressure has been shown to differ significantly *in the various parts of the loop* The collecting venules anastomose with one another to form the subpapillary venous plexuses which in turn drain into the deeper veins For detailed correlation between anatomy and physiology of the minute circulation the reader is referred to the special section of this book (Part V)

The entire vascular tree is innervated by the autonomic nervous system Vasomotor impulses are controlled by vasomotor centers (a vasoconstrictor and a vasodilator center) that are located bilaterally in the floor of the fourth ventricle There is evidence that higher vasomotor centers are found in the hypothalamus and even in the cerebral cortex[13] Vasomotor nerves consist of vasoconstrictor and vasodilator fibers The constrictor fibers arise from nerve cells in the lateral horns of the eighth cervical or first thoracic to the second or third lumbar segments of the cord (often referred to as the thoracico lumbar outflow which constitutes the sympathetic division of the autonomic nervous system) These preganglionic fibers emerge from the cord through the *anterior roots of the thoracico* lumbar spinal segments as fine medullated fibers from which they soon separate together with other somatic medullated motor fibers *to enter the corresponding ganglia in* the vertebral sympathetic chain through the white rami communicantes These preganglionic *fibers synapse with cells in the corre*sponding ganglia as well as in those of other levels Postganglionic fibers which are nonmedullated arise from all the vertebral *ganglia and join the spinal nerves through the* gray rami communicantes They continue peripherally and are distributed to the various parts of the body together with the other *(somatic) fibers in the spinal nerves Vaso*constrictor impulses *to* the blood vessels of the upper extremities are conveyed through preganglionic fibers emerging from the first *through the eighth or ninth thoracic segment* of the spinal cord synapsing with the cells in the vertebral sympathetic ganglia and transmitted through postganglionic fibers arising *from the middle and inferior cervical and first* and second thoracic ganglia Vasoconstrictor impulses to the vessels of the lower extremity are conveyed through preganglionic fibers emerging from the tenth thoracic and first and second lumbar spinal segments and through the ganglia by way of postganglionic fibers from the twelfth thoracic through the fourth sacral ganglia These nerves are distributed to the vessels segmentally In the upper extremities postganglionic nonmedullated fibers from the middle and inferior cervical ganglia pass to the subclavian artery where they form a plexus like structure in the outer coat of the vessel and its branches including the axillary artery These fibers which constitute the proximal innervation of the vessels do not extend beyond the proximal portions of the brachial artery Distal parts of the vessels are innervated by postganglionic nerve fibers which are conveyed by way of the (somatic) nerves of the brachial plexus These fibers terminate at various levels in the arteries up to and including the arterioles and capillaries In the vessel wall the *same fibers form three distinct plexuses one* in the outer coat or tunica adventitia another in the muscular and a third between these two layers Similarly in the lower extremi

In general the sympathetic vasodilator fibers are cholinergic their action is mediated through the liberation of acetylcholine In some species adrenergic vasodilator fibers have been demonstrated the relationship of the transmittor substance (acetylcholine) liberated upon their stimulation to the adrenalin like substance mediating vasoconstriction is unknown

Investigation of the respective roles played by the cerebrospinal and autonomic systems seems to indicate that the sympathetic pathways and in particular the adrenergic fibers are outstandingly responsible for maintaining arterial vessels in general at a certain degree of constriction this is supposedly expressed in tonicity of the vessels and thus the term vasomotor tone has become well established[13]

Increased vasomotor tone is consequently associated with vasoconstriction while vasodilatation represents a state of relaxed vasomotor tone While the foregoing hypothesis is applicable to the arterial part of the circulation it is not as well established for the venous system[5] and it can hardly be applied to the minute circulation where neither the existence of contractible elements or sympathetic nerve fibers has been conclusively proved

The neural mechanism seems to dominate vascular beds in varying degrees It seems that the skin bed is almost entirely controlled by it but this does not apply to the skeletal muscular bed[33] or to the vascular bed in the liver[34, 35] To what extent it controls blood flow to the kidneys and the heart is not yet known Cerebral flow seems to be quite independent of autonomic vasomotor control

2 Humoral In the light of increasing knowledge of neurohumoral transmission a separation of this type of controlling mechanism from the plainly neural becomes difficult However the occurrence of vasopressor and depressor substances and the proven vasomotive action of certain known endocrine secretions including the demonstrable effects of the catecholamines adrenaline and noradrenaline make such separation mandatory[39, 43]

A vasomotor effect of humoral factors not directly related to the function of the neural mechanisms seems therefore demonstrable only on the minute circulation Recognition of the possibly great importance of the action of catechol amines or other humoral agents in the vasomotor mechanism concerning larger caliber vessels hinges on further investigation Such investigation should be—and no doubt will be—directed at (1) proving or disproving the existence of an enzymatic mechanism of neurohumoral transmission of vasomotor impulses to the smooth muscle coat of arterial vessels similar to that proven for the neurohumoral transmission of motor impulses to skeletal muscles and (2) determining the role of any of the catechol amines in such a mechanism

3 Metabolic Since the classic demonstration of the triple response[44] and the assumption of the existence of metabolites acting as H like substances no further real advance has been made in clarifying the substrates of a metabolic vasomotive mechanism It is by quite indirect methods that it can be demonstrated that blood flow through skeletal muscles in man seems to depend upon work performance rather than upon sympathetic innervation[9, 33, 4]

VASOMOTOR STIMULI

Vasomotor responses may be elicited essentially in two ways either directly or via a reflex When assessing the effects of stimuli producing a change in vessel caliber it is necessary to realize that generalized or unidirectional responses of the vascular system as one entity cannot and do not exist The responses of various vascular beds may differ either quantitatively or qualitatively depending upon the nature of the stimulus,[5, 8, 34, 36, 40, 49] where a part, such as an extremity contains more than one vascular bed, it becomes necessary to take that differentiation into account when assessing blood flow to the

their lumina by way of contraction (constriction) of this circular coat of smooth musculature and widen their lumina by way of relaxation of it.

This assumption cannot be made with the same ease concerning vessels of venous type. There, the smooth muscular coat is thinner and arranged in a more complicated manner and the testing of vasomotion is still more difficult than on the arterial side.[1]

The question of the existence of active vasomotion in the vessels representing the minute or capillary circulation which is devoid of either elastic tissue or muscular elements has been debated for decades. While narrowing or widening of the lumina of minute blood vessels has been observed and demonstrated,[3] the evidence seems to indicate that vasomotion here is mediated through a mechanism that is different from those that activate the arteries. It appears that narrowing and widening of the lumina in minute blood vessels are brought about respectively by swelling and flattening of the cells comprising the endothelial tube, with the role of the cementing substance to be still more definitely established.

Just as the structural process taking place during vasomotion is different in the three main parts of the vascular tree, so its physiologic significance is obviously different. If effected on the arterial side, constriction means curtailment in supply of oxygen and nutrients while dilation means the opposite. On the venous side, vasomotion might be expected to influence drainage from the part; in the minute circulation, constriction logically suppresses metabolic exchange, while dilation enhances it.[3, 4]

Since these differences exist concerning the vasomotive process in the three main parts of the vascular tree, various combinations of narrowing and dilation may be expected to occur under varying conditions. A further complication arises from the fact that the vascular supply to a specific organ or organ system usually responds as a physiologic unit. These units, for which the term vascular bed is used, are largely independent, more or less, in their vasomotive responses.[13, 2, 26] *Thus one and the same stimulus may simultaneously produce constriction in one vascular bed and dilation in another, while failing to produce any response in a third.*[27]

THE MECHANISMS INVOLVED IN VASOMOTION

In general, a response in a target organ may be elicited in as many ways as there are mechanisms by which the stimulus or stimuli are conveyed to it. Where more than one mechanism is working at any one time, the net response depends upon whichever of these mechanisms is most active at that time. Three types of mechanism are known to play significant roles in controlling vasomotive responses.

1. Neural. The best known and most extensively studied of these mechanisms is one mediated by the nervous system—through the vasomotor nerves. There are two types of vasomotor nerves: the vasoconstrictor nerves, which cause contraction of the arteriolar musculature, and the vasodilator nerves, which inhibit the former and thereby cause relaxation of the muscular rings. Vasoconstrictor fibers *reach the arterioles by two distinct routes* (Todd & Kramer; Woollard): through the *sympathetic fibers of the autonomic nervous system (which fibers do not extend beyond the larger vessels of the limb) and through* sympathetic fibers which run with the somatic *nerve trunks (reaching the arteries at different levels down to its smallest branches).* There is good evidence to indicate that vasoconstriction is in all probability mediated *through the liberation of an adrenalin-like* substance at the nerve endings.

The sympathetic vasodilators are of two types: those which bring about their effect by *the liberation of acetylcholine (cholinergic* fibers) and those whose action is mediated by *an adrenalin-like substance (adrenergic* fibers). The presence of sympathetic vasodilators *in the human skin is in dispute.*[4-8]

Chapter 2 Evaluation of Blood Flow

The measurement of rate of blood flow to an organ or organ system lends itself to many uses the primary one being as an index of the functional capacity of the organ By the same token it is used to estimate the degree to which such function has been affected by certain disease states or how it may be influenced by certain therapeutic measures whether the latter be designed precisely to correct a vascular derangement or administered for other purposes

Applied to the extremities measurements of blood flow are used for diagnostic prognostic and therapeutic purpose Various elaborate methods have been designed for this purpose each one in turn having been described as accurate and precise only to be shown subsequently to fall short in one way or another of what was expected of it These methods are of considerable investigative interest and will be described in detail but they have not replaced certain clinical tests and procedures The simple clinical approach that still retains its place in the armamentarium of the clinician as well as the investigator will be taken up first

CLINICAL METHODS 1 HISTORY AND PHYSICAL EXAMINATION

The clinical history of the condition must be taken and the general physical examination of the patient done with the same thoroughness as with other diseases Many systemic dermatologic neurologic and orthopedic diseases may manifest themselves in the extremities mimicking conditions that seem attributable primarily to vascular disturbance Detailed differentiation in that respect is not within the scope of this book the reader is referred to the textbooks in the various fields There are some symptoms and signs which must be investigated in greater detail because of their association with circulatory disturbances These symptoms include pain claudication fatigue and such sensory disturbances a burning numbness tingling and feeling of cold

Pain Important details to look into are (a) its exact location in respect to the extremities involved (b) its onset whether insidious and progressive or sudden and acute (c) its character—it may be a discomfort or a pain of varying description (d) its severity which may range from an abnormal sensation to excruciating intractability (e) the circumstances that provoke its appearance—it may follow a traumatic injury or occur in the wake of another systemic disease it may be provoked or exacerbated by effort or exercise or it may appear even at rest it may be produced by assuming certain positions it may appear at certain time under certain climatic conditions and (f) the circumstances that bring about its relief or alleviation—rest or exercise heat or cold change of position or certain drugs In general pain due to vascular disturbances is attributed to anoxia of or the accumulation of metabolite in the tissues In some instances it is attributed to neural disturbances resulting from interference with the blood supply to nerves

Intermittent Claudication This term has been widely used to denote a symptom which when present if properly ascertained is pathognomic for arterial insufficiency The classical intermittent claudication is a cramplike pain usually in the lower extremitie brought about or intensified by walking especially if done rapidly or by climbing up stairs and promptly relieved by rest The location of this pain depends upon the vessel involved For example occlusion of the aorta at its bifurcation (Leriche s Syndrome) causes localization of the phenomenon in the hip or hips while the common site of occlusion at the popliteal branching produces it in the calf In some case the patient complain of pain at rest occurring often in his sleep which is relieved by his getting out of bed and massaging the part This indicates a more advanced pathologic state of the vessel in question The parallel to angina of effort and angina decubitus is striking

part[50 5] From the differences in morphologic structure as well as in functional performance it might be expected that the three main parts of the vascular tree also differ in their responses to stimuli [1 3 3]

1 Physiologic Stimuli Changes in environment primarily affect the vascular bed in the skin In general cooling produces vasoconstriction, while warming produces vasodilation in both arterial and minute vessels [8 41 4 56] Heat production in the body and vasomotor responses in the vascular beds of the *integument are governed by physical, nervous* and neurohumoral mechanisms in such a manner as to maintain body heat within physiologic limits When the body is exposed to excessive cold increased heat production and vasoconstriction of the surface vessels occur Excessive heat production is followed by vasodilation of the surface vessels and increased heat loss [13 57 9] Deep inspiration causes reflex vasoconstriction of the cutaneous vessels [13] In the animal experiments stimulation of the mesentery peritoneum and abdominal viscera is followed by a vasodilator response and fall in blood pressure In patients with high thoracic and cervical transection of the cord distension of the urinary bladder and other abdominal viscera evokes vasoconstriction of a patchy type in the toes and fingers and a marked vasodilation in the upper trunk shoulder face and neck While there is marked vasoconstriction in the vascular bed of the skin of the fingers the blood flow in the vascular bed of the muscles of the forearm is greatly increased In low transection of the cord there is vasoconstriction in the lower limbs including the toes and vasodilation above the level of the lesion especially the fingers [6] During sleep there is a decreased heart rate decreased cardiac output peripheral vasodilation and reduced blood pressure In sleep that is disturbed with exciting dreams however there is increased heart rate elevated blood pressure and peripheral vasoconstriction [61] Pain evokes a pressor response This may be mediated through the excitation of psychic centers and the liberation of adrenaline by the painful stimuli [13] Work and exercise, at their very inception cause constriction of the splanchnic vessel During exercise there is vasodilation of the vascular bed in the muscles resulting from local action of the metabolic products formed in the muscles themselves Cutaneous vasodilation and possibly a reduction in the degree of splanchnic vasoconstriction occur as the exercise continues [13] *Psychogenic stimuli such as* anger or fear may cause cutaneous vasoconstriction mediated through hormonal mechanisms On the other hand embarrassment causes the familiar blush also mediated through *central nervous pathways Blushing is caused by* vasodilation of the most superficial minute vessels in the blush areas of the body notably the face neck upper chest and sometimes on the hand and feet *Its occurrence however* does not necessitate the presence of vasodilation of the larger arterial channels and hence does not indicate an increase in blood flow to the part as a whole Flushing results from passive distension of the minute vessels and may occur when the arterial flow is increased when the venous drainage is obstructed or when the minute vessel lose their tone Like blushing flushing may occur without vasodilation of the main arterial channels and increase of blood flow to the part may be present without producing the flush or the blush [6]

2 Pharmacologic Stimuli Various drugs have been used to produce vasomotion In some of them there is good experimental evidence to show influence upon the blood vessels in others such evidence is lacking but clinical experience has proven their usefulness [63] A vasoactive drug may produce vasodilation in one vascular bed and vasoconstriction in another a drug may be vasoactive in one part of the vascular tree and inert in another segment a drug may cause dilation in one concentration and constriction in another [63] It therefore appears that the use of the terms vasodilator or vasoconstrictor drugs is misleading since these terms would connote a universal effect Designation of a drug as vasoactive in one direction or the other seems possible only in connection with *specific data as to site and modalities of its* action

motor and vascular disorders and may be their presenting manifestation. In arterial insufficiency blanching is easily induced by elevation of the part, while in vasomotor disorders it may be produced by exposure to cold or by some emotional disturbance. Sudden pallor of an extremity is a common finding immediately following embolic or thrombotic occlusion of the arterial channel supplying the part. Pallor as part of a generalized condition such as in various anemic states must of course be ruled out.

Cyanosis, a bluish dusky discoloration of the skin, results from deficient oxygenation of the blood. As such, generalized cyanosis occurs whenever arterial oxygen saturation is subnormal, as in states of respiratory or cardiac failure. Localized cyanosis, on the other hand, suggests inadequate or slow circulation in the part as a result either of vasospasm or impairment of drainage with local pooling in the minute vessels. Cyanosis occurring in vasospastic states is transient. In occlusive vascular disease it may occur transiently as part of a sequence of color changes—pallor on elevation which persists for the first few seconds on dependency of the limb, followed sooner or later by redness that deepens to a purple hue and is commonly referred to as "rubor on dependency." Persistent localized cyanosis as a rule indicates a more serious or more permanent vascular disturbance. When a persistent cyanosis develops rapidly to a marked degree and is associated with coldness of the parts involved, it usually portends a very grave situation, impending gangrene.

d. Skin Lesions. Lesions due to dermatologic conditions are not considered here. *Hemorrhagic extravasations*, e.g., petechiae and purpura, may be seen in acute thromboarteritis, polyarteritis (periarteritis nodosa) and thrombotic microangiopathy. Large cutaneous sugillations at pressure points are not uncommon in elderly arteriosclerotics; they have been called "senile purpura."[63]

Ulcerations per se do not constitute prima facie evidence of vascular insufficiency. Those due to specific etiologies must be ruled out. However, if they occur or recur following minimal trauma, or if they show no tendency to heal despite their apparent small size, or if they present gangrenous changes, a so-called "ischemic ulcer" with vascular impairment as the underlying physiopathology must be considered.

Nodules may be felt under the skin in patients with polyarteritis (periarteritis nodosa). There distribution more or less along the course of the arteries may be of diagnostic significance. This is established by biopsy. Nodules of various appearance are seen in the skin (a vascular tumor), erythema nodosum (a sensitivity reaction) and several conditions not directly related to vascular disease.

Blebs. Patients with vascular disease are prone to develop blebs and blisters because of burns, scalds, or undue exposure to heat. Also in areas with moist gangrene resulting from acute arterial occlusion blistering is common. However, patients with arterial disease sometimes develop blebs spontaneously; these present very characteristic features well described by Kramer.[64] They appear suddenly and develop rapidly, usually overnight, and frequently are fully developed when first noticed. Association with trauma or the other common causes is denied. They most commonly occur on or about the toes, ranging from 1 cm to 6 cm in diameter. The inflammatory reaction is minimal and, except for slight itching, burning, or minimal pain, they are for the most part symptomless. The fluid content is at first clear and colorless, becoming turbid and discolored, but not frankly purulent, within 24 to 48 hours, after which time a smaller or greater area of gangrene is seen at its base. The subsequent course is that of a gangrenous lesion. Occasionally we have seen such blisters filled with dark hemorrhagic fluid.

2. Palpation

a. The peripheral pulses. It is customary to palpate for the brachial and radial pulses in the upper extremities and for the femoral, the popliteal, the posterior tibial and the dor

Fatigue This symptom may be very significant if it specifically affects the extremities, if it is related to effort and if it recurs persistently As Kramer[84] points out, it may be the first indication of beginning vascular disease Fatigue as part of the clinical picture of a systemic disorder or due to a neurologic disease must, of course be ruled out

Burning Numbness Tingling Coldness Sensory disturbances usually associated with neurologic disorders are frequently seen in patients with vascular disease A burning sensation or burning pain may be complained of by patients with such divergent disorders as erythermalgia thromboangiitis obliterans or obliterative arteriosclerosis The phenomenon however is specially characteristic for erythermalgia a vasodilator disorder associated with redness and warmth of the part aggravated by dependency of the extremity or by application of warmth and relieved by elevation of the part and cold In thromboangiitis obliterans and obliterative arteriosclerosis on the other hand there may be some color changes but the part is cold to the touch and the symptom if anything is aggravated by elevation of the extremity

Numbness and tingling are common complaints but they are frequently overlooked because as an isolated complaint they are usually attributed to some neurologic disturbances while as an associated symptom they are mostly overshadowed by pain or burning Attention has been called to their occurrence preceding pain and other signs and symptoms of sudden arterial occlusion

The subjective feeling of coldness is very common in occlusive vascular disorders However in the absence of any other manifestation its significance is questionable The part may even be actually cold to the touch and yet there may not be any demonstrable vascular pathology Disappearance of coldness following treatment however may be the first indication of an improved circulation in patients with established arterial insufficiency

In describing the physical findings an attempt will be made to classify them according to the branch of the vascular tree apparently involved the arterial the minute or the *venous circulation*

THE ARTERIAL CIRCULATION

1 Inspection

a Asymmetry of the two sides The two sides are unequal in the presence of arteriovenous fistulas the involved limb being larger than its fellow in one or more dimensions Another condition causing undue enlargement of *the involved limb is unilateral lymph stasis as* in elephantiasis Limbs surviving arterial occlusion without the development of gangrene usually show some muscular atrophy Extravascular conditions causing asymmetry of the *limbs are neurogenic muscular atrophy (e g* in poliomyelitis) and disuse resulting in decrease in size of the limb or neoplastic conditions causing its enlargement

b Condition of the Skin and Its Appendages In long standing arterial insufficiency one may note considerable atrophy of the subcutaneous tissue Abnormalities of the nails (hypertrophic stunted or deformed brittle lusterless) and hair (scanty thin lusterless and brittle) are very common Specific changes producing a tight waxy atrophic skin are seen in scleroderma and to a certain degree in Raynaud disease

c Color Changes Erythema or redness in varying shades may be seen in the distal parts of an extremity or in some of its digit involving the greater part of an extremity both upper or both lower extremities or some other pattern Purely dermatologic conditions must be considered and subsequently ruled out Aside from the localization of the finding—and whether it is transient or permanent—associated symptoms (burning pain etc) the presence of coldness or warmth of the involved part and the conditions that excite or aggravate it (exposed to cold warmth dependency of the part emotional disturbances) must be considered

Pallor or Blanching like redness and cyanosis is a very common finding in vaso

lated capillaries and angiomata which are benign vascular tumors do not cause clinically significant disturbances in blood flow

THE VENOUS CIRCULATION

Color changes It has been shown that barring the naturally occurring pigment the color of the skin is normally dependent upon the amount and color of the blood in the subpapillary venous plexus (a rich plexus formed by the anastomosis of numerous collecting venules which in turn are formed by the union of several venous limbs of adjacent capillary loops) instead of that in the more superficial capillary loops[44] An explanation offered for this is the anatomical fact that the plexus presents a greater area parallel to the skin surface compared to the capillary loops which are mostly disposed at right angles to it[13] Lewis demonstrated that pressure applied to the skin produces first collapse of the venous plexus which in turn causes blanching this is not appreciably increased by subsequent compression of the capillary loops through further pressure[44] It is very likely that the vasomotive capacity of the collecting venules and subpapillary venous plexuses is even poorer than that of the terminal capillary loop Measuring the gradient of pressure in the capillary loop Landis[66,67] found that this was least in the venous limb the average pressure at that segment being only about half that found at the summit of the loop These findings suggest that vasomotion in these venules and venous plexuses is more or less passive in response to the hemodynamic forces at play in the arterial (and capillary) system as well as in the rest of the venous tree Hence they distend whenever the arterial inflow exceeds the venous outflow and collapse when the reverse takes place reflecting to a certain degree the vascular status of the part observed

It should be noted in view of the above that by and large pallor or blanching redness or erythema and cyanosis though manifested through the initial segments of the venous system actually reflect only the pathologic and physiopathologic responses taking place primarily in the other portions of the vascular tree They do not occur as a result of organic or functional disturbances in these vessels proper but merely as a passive reaction to hemodynamic forces in the arterial circulation (vis a tergo) and the rest of the venous system (vis a fronte)

Cyanosis The basic cause of cyanosis is subnormal oxygen saturation of the blood As mentioned in a previous section it may be seen in certain arterial diseases Obviously in venous disorders that cause damming back or sluggishness of the circulation as in venous obstruction cyanosis may be a prominent feature this of course applies equally to congestive heart failure where there is a generalized impairment of venous return A benign condition characterized by an intense localized cyanosis involving predominantly the big toe and attributed to venospasm has been described[64]

Erythema Localized erythema forming part of the picture of inflammation, may be seen in phlebitis or thrombophlebitis involving the superficial veins Thrombophlebitis involving deep veins may not exhibit any superficial erythema but rather palpable tender cord with infiltration and edema of the surrounding tissues

Edema This results from the exudation or escape of fluid from the minute circulation into the intercellular space It occurs in the presence of unduly increased intravascular pressure increased permeability of the vessel wall or physico chemical disturbances in the composition of the blood Localized edema occurs following venous obstruction primarily because of the resulting congestion and increased intravascular pressure and in all probability also from increased vascular permeability Lymphedema is a brawny infiltration of the intercellular spaces due to lymph stasis following obstruction of the lymphatic channel In longstanding venous obstruction especially that involving the large venous trunks lymph stasis is superimposed on the edema sooner or later

salis pedis artery (or its proximal part, the anterior tibial) in the lower extremities The presence or absence of pul ation and its forcefulness are noted the presence of sclerotic changes by the hardnes elasticity or beading of the arterial wall is ascertained The presence of strong pul ations indicates adequate main stem or primary circulation at the point of its detection Its complete absence may indicate an embryologic anomaly or malformation or an obstructive process involving a proximal egment of the primary arterial channel We are using the term primary arterial channel advisedly instead of referring to the regional circulation as a whole Complete absence of a peripheral pul e even if resulting from obliterative arterial disease is no absolute gauge of the adequacy of the over all circulation The primary arterial channel may be blocked but there might be sufficient econdary or collateral channels to maintain an adequate blood supply to the distal p rts Periodic disappearance of the pulse is characteristic of vasopastic states Diminution in forcefulness of a pul e previously noted to be normal is usually indicative of a developing arterial obstructive pathology The permanent disappearance of a previou ly palpable pulse is a diagnostic feature of embolic or thrombotic occlusion An abnormally located pul ation may be felt over well developed collateral ves els when the normal primary channel is ob tructed An abnormally located pulsation associated with a thrill a bruit and/or a murmur is a common finding over arterio venous fistulae if the e are encountered over a ma s which al o exhibits pul atile expansion they are almo t pathognomonic for an arterial aneurysm

b *Changes in Surface Temperature* Coldness of extremities if bilateral and symmetrical may be a normal finding Even marked coldnes may be an expre sion of a primarily neurologic rather than a va cular disturbance In these cases aside from the di tribution and the absence of symptoms there is often as ociated hyperhidrosis On the other hand bilateral and symmetrical coldness may be found in va o pastic and in occlusive vascular di orders occurring transiently in the former and persistently in the latter Aside from concommitant color changes there are usually associated symptoms of vascular insufficiency

Coldness of one extremity or parts of it, evaluated best by comparison of it with the other side, is almo t invariably a manifestation of vascular pathology which may again be either vasospastic or occlusive in nature one being distingui hable from the other by the associated signs and symptoms

Warmth as a localized physical finding by and large implies the presence of inflammation In uncomplicated obliterative vascular conditions despite an associated finding of redness or erythema and the complaint of a burning sen ation, the involved parts are cold to the touch In these ca es warmth or heat indicates an inflammatory reaction to a complicating secondary infection

The only va cular disturbances exhibiting abnormal warmth in the involved parts in the ab ence of inflammation are arteriovenous fistulae and erythermalgia the latter characterized by usually bilaterally and symmetrically warm red and burning extremities

3 Percussion and Auscultation

The e methods of physical examination are very rarely u ed in the detection or evaluation of vascular pathologic conditions An exception is the confirmatory finding of a bruit or murmur on auscultation over the su pected site of an arteriovenous fistula or an aneurysm

THE MINUTE CIRCULATION

Petechiae and Purpura Minute extravasations of blood may occur as a result either of embolic phenomena infectious or noninfectious or capillary wall damage (defect in intercellular cement substance) While the e lesions may occur in pathologic tates where there is a va cular di order they do not nec es arily reflect the extent or the magnitude of that disorder

Telangiectasias which are abnormally di

ing of the selected vein the limb is lowered to the horizontal position and the time for refilling of the selected vein is noted. Normally this takes 5 to 15 seconds; a delay indicates impaired arterial inflow. Obviously the test as described is of no value in the presence of varicose veins with defective valve and venous insufficiency due to consequent backflow of blood. However, where the defect is limited to the *superficial set of veins (not involving* the deep set or the communicating veins) the test may still be of value if the backflow of blood is prevented by placing an easily removable rubber band around the leg just below the knee before the limb is lowered in *order to occlude venous circulation.*

e. Reactive hyperemia test. The limb to be tested is elevated until the vessels are emptied of their blood content as evidenced by maximal blanching produced (this is best appreciated on the palmar or plantar surfaces). A cuff or tourniquet is then placed high on the limb and pressure above the systolic is applied to occlude arterial circulation. The limb is then lowered to the horizontal level and the pressure released. The time it takes for the blush (reactive hyperemia) to occur is noted as well as the time it takes for the normal color to set in. A more elaborate test utilizing this principle is described by Pickering.[4]

f. The arterial pressure. Direct measurement of arterial pressure involves the intro*duction of a medium sized needle into the* arterial lumen; the systolic and diastolic pressures are registered by a manometer attached to the system. There are a number of instruments available that permit direct recording of the pressures.

*The indirect method using the sphygmo*manometer (Riva Rocci) is based on the principle that the pressure necessary to suppress flow in an elastic tube is about identical with the pressure under which flow through the vessel occurs. A pressure cuff is placed around the limb and *inflated until interruption of flow* through the artery has been ascertained. The point at which blood flow is resumed is the moment when intra-arterial pressure equals the applied pressure. This can be detected by the appearance of an auscultatory sound with each pulse wave over the portion of the artery just distal to the obstruction when the cuff is slowly deflated. The value of the applied pressure at the first appearance of a sound is taken to be equal to the systolic pressure. On further deflation of the cuff the sound changes in character and finally disappear. This end point is recorded as the diastolic pressure. Steele[5] has shown that this best approximates the directly recorded diastolic pressure. The direct method is superior as far as objectivity and accuracy are concerned. However, for daily practical use the indirect method is perfectly adequate.

g. Radiography, Aortography and Arteriography. With plain radiography the presence of calcification in vascular walls is visualized. This procedure alone, however, does not pro*vide the examiner with any information as to* the patency of the vessel, the presence or absence of obstructive pathology or the presence (let alone extent) of compensatory collateral channels. More information, however, including that concerning the exact site of the ob*struction, may be obtained through the use* of radiopaque substances. These are injected percutaneously or through a cut down into the artery, then visualized radiologically as they course through the various arterial branches. The substance may be injected into *the aorta* (aortography) or into the smaller arterial trunks (arteriography). Various substances have been employed for this purpose. Diodrast, Neo Iopax and Swedish Umbradil have been found most satisfactory.

TESTS FOR THE MINUTE CIRCULATION

a. Postural Color Changes and Reactive Hyperemia. While postural color changes and reactive hyperemia are used as gauges of competency of arterial channels, the reaction actually observed as previously mentioned consists in *changes produced in or reflected by* the minute circulation. In a broader sense therefore wherever such a test can be per

Varicose Veins Varicosities of the superficial veins are easily seen and palpated as prominent, engorged and tortuous "worm like" structures just beneath the overlying skin but raised beyond its level Varicose veins are usually the result of congenitally weak valves and vessel wall incompetence of the valves of the deep and/or communicating veins or the presence of arteriovenous fistulae, they may represent extensive collateral channels following obstruction of main venous trunks

Varicose or Stasis Ulcers Findings characterizing these ulcers are aside from their indolence and resistance to treatment, the sequelae of prolonged venous stasis increased pigmentation edema and often the presence of superficial varicose vein These ulcers are distinguished from ulcers due to specific causes trophic or pressure sores and ischemic ulcers

CLINICAL METHODS 2 TESTS AND PROCEDURES

There are numerous clinical tests and procedures that are employed to determine the competence or adequacy of the circulation in the extremities Some are very simple while others are relatively complicated the ease or difficulty of their performance being no index of their relative clinical usefulness These procedures will be described briefly grouped according to the portion of the vascular tree they are intended to test

TESTS FOR THE ARTERIAL CIRCULATION

a Postural Color Changes[68,70] Characteristic color changes may be produced at will in limbs with arterial insufficiency With the patient lying on his back elevation of the leg and foot produces blanching of the part best appreciated on the plantar surface of the toes and the soles of the feet When the patient sits up with his feet dangling down the side of the bed the pallor is sooner or later replaced by a reddish or purplish erythema that may be diffused or mottled in appearance In normal persons with unimpaired arterial circulation, slight blanching may occur on elevation this will give way to normal color within 30 seconds on dependency In the patient with arterial insufficiency, return of normal color on dependency is either considerably delayed (1 minute or more) or the pallor is immediately replaced by rubor, as described above

b Postural Pain This if present accompanies the postural color changes With elevation of the limb the action of gravity further depletes the already insufficient arterial blood supply to the part causing the blanching previously described and at the same time producing pain

c Changes on Exercise If the patient is lying on his back with his limbs elevated he is made to exercise by alternately flexing and extending his ankles and toes (or wrists and fingers) 10 to 60 times per minute Blanching (plantar ischemia test)[71] and pain increase in the presence of marked arterial insufficiency while in its absence or in well compensated cases normal color may be restored through exercise

Claudication Time The patient is made to walk at a regular fast pace (120 steps/min) or to climb a flight of stairs until pain or claudication appears The time that elapsed from the start of the test to the appearance of the pain is noted as the claudication time A treadmill or a physiologic bicycle have been used for the same purpose

Claudication Distance The test is performed as above except that the distance rather than the time before claudication occurs is measured as a criterion

Kisch Test Again either claudication time or distance may also be determined with the patient lying flat on his back and exercising the limb from this position by rhythmically flexing and extending the extremity at a rate of 30 times per minute

d Venous Filling Time[7] One of the prominent superficial veins on the dorsum of the foot is watched carefully With the patient in a supine position the limb is elevated to drain the veins of their blood content After empty

rounding flare and wheal formation The red reaction is a red band which appears shortly (3 15 econd) after stimulation on the line of troke Pale lines on both sides of the red band may also be een Both reactions appear to result from direct timulation of the capil lary wall which cau es dilation of the ve sel where the mechanical timulus was greater and con triction where the stimulation was less inten e Their appearance is not dependent upon nervous mechani ms or the tatus of the larger va cular channels If the stimulus is greater in intensity or is applied repeatedly a flare or a preading flu h tarts to surround the local red reaction shortly afterward it is outla ted by the local reaction The flare re sults from arteriolar dilatation due to an axon reflex et in motion by the stimulus Occlusion of the arterial circulation prevents the occur ence of the flare Upon still more intense or repeated mechanical stimulation a blanched and raised lesion appears at the site of the red reaction completely replacing it (wheal formation) The lesion at first harply de marcated from the surrounding normal skin oon spread out and decreases in height grad ually disappearing after a few hours The wheal results from a localized increa ed per meability of the capillary wall and its produc tion is not dependent upon a nervous mechan ism

Lewis has demon trated convincingly that this triple re pon e results from the produc tion of a histamin like substance by the under lying cells The action of these substances is very similar to that of hi tamine which al o produces the triple response when injected intradermally This production of an H like sub tance has similarly been invoked to ex plain the cutaneous reaction ob erved follow ing various physical stimuli such as burning freezing electrical stimulation etc as well as tho e which compri e the cardinal signs of in flammation This is al o true of the cutaneous le ions ob erved in disturbances of the pos terior or sensory root of the central nervous ystem (via anti dromic impulses)[91] They are con idered the basic va cular lesion in allergic re ponses This concept assumes the presence of a neuro humoral mechanism with hista min like sub tances respon ible for the red reaction and wheal production by direct action on the capillary wall and acetylcholine[92] re lea ed by the excitation of the axon reflex re sponsible for the arteriolar dilation that causes the flare

g Saline Wheal Test When physiologic saline olution (0 2 cc of 0 85% olution) is injected intradermally a wheal is produced at the site of injection Normally this wheal dis appears in 30 to 60 minutes It has been dem onstrated that in the presence of vascular di ease there is considerable reduction of the di appearing time[93 95] A flaw in this test is the need to make multiple inoculation sites— a very inconvenient procedure for the patient Evaluation of the te t s actual significance is difficult because of the many nonva cular fac tors influencing absorption

TESTS FOR THE VENOUS CIRCULATION

a Postural Changes In the presence of ve nous in ufficiency resulting from deep venous occlusion with or without varico ities swelling or edema of the extremity is produced or ex acerbated by dependency and relieved by ele vation of the part Similarly pain that is usu ally characterized as a dull ache or a heaviness may be experienced on dependency of the part or after prolonged standing Relief is obtained by recumbency or elevation of the part

b Tests for Venous Insufficiency (Presence of block or of incompetence) Localized ve nous insufficiency results from obstruction or narrowing (secondary to thrombophlebitis) or from weakened vascular walls or incompe tent valves (main cau es for the development of varicosities) These pathologic conditions may involve either the deep or the superficial veins In the presence of superficial varicose veins localization of the exact source of venous backflow is nece ary In the deep venous sys tem varices hardly occur but incompetency of the valves may be encountered The most fre quent cause of insufficiency of the deep veins is

formed at all the capillary system must be adequate or competent

b Capillary Pressure A method to measure blood pressure in individual capillary loops by micromanipulation inserting a glass canula into either of its limbs has been described by Landis[66] He reported changes in capillary pressure produced by altering the distance (level) between the heart and the vessel being examined the application of heat venous congestion production of a histamine flare application of cold and in *Raynaud's* disease[17] This procedure does not find clinical application *because of the need for very* specialized apparatus and technical skill In*direct methods using a micro capillary tonom*eter measure either the amount of pressure *that empties or the pressure* that permits refilling the capillary loops as observed under a capillary microscope

c Capillary Resistance Rumpel Leede's test A tourniquet or a sphygmomanometer cuff is placed around the arm and positive pressure to obstruct venous return is applied midway between the systolic and diastolic pressures for 10 minutes The number of petechiae appearing in a selected area distal to the obstruction (usually in the forearm) is noted The degree of capillary resistance is taken to be inversely related to the number *of petechiae produced*

Hecht Dalldorf's test In this procedure the *production of petechiae is induced by the ap*plication of negative pressure to the skin This *is done by means of a vacuum pump connected* to a small suction cup that is applied to the skin *for one minute Capillary resistance is* measured and expressed in terms of the least *negative pressure required to produce pe*techiae This test can be very easily performed *with a petechiometer a simple apparatus con*sisting of a bell connected with a suction syringe *arrangement Attempts to quantitate the* test have not met with impressive success

d Capillary Microscopy A drop of cedar oil placed on the skin renders the surface homogeneous and transparent enough to permit *visualization of capillaries and the blood flow* through them by opaque illumination with *a strong light* under a microscope (Lombard)[78] The capillary system may be thus visualized at any place in the integument including the accessible mucous membranes (lip cheek gums conjunctiva) The number size and configuration of the loop the relationship between its arterial and venous limb the velocity and character of the blood stream through it and the response to the various stimuli may best be observed at the nail bed where the individual loops are long and run horizontally The conjunctival capillaries may likewise be observed with the use of the slit lamp microscope The possibilities of this procedure as a diagnostic tool are questionable despite *reports in the literature* describing abnormalities in the capillary loops associated with various diseases[8 86] *Consequently* in spite of its relative simplicity the procedure has not found the *clinical application it pos*sibly deserves because a basis of correlating *the sometimes intriguing morphologic varia*tions with known clinical entities is practically *non existent*

e Histamine Flare[44 87 90] When histamine (1 1000 acid phosphate solution) is pricked or injected (0 1 cc) intradermally a wheal and a surrounding flare develops at the site of inoculation The reaction is prompt beginning in 2 minutes and ending within 10 minutes A delayed or poor development of the reaction has been interpreted to signify an impaired circulation in the area tested Since the wheal results from a direct action on the capillary wall while the flare appears to result from arteriolar dilatation produced through an axon reflex the wheal is more significant than the flare in view of the fact that the production of the latter may be influenced by the presence of some nervous disorder

f Lewis Triple Response[44] If the skin is stroked firmly with a pointed instrument the following reactions may be *elicited depend*ing upon the intensity of the stimulus a *red* reaction *(vasodilation) followed by a sur*

walking alone (without the tourniquet) is also observed At those levels where application of the tourniquet followed by exercise is not associated with appreciable change in the filling of the veins it is presumed that the communicating and deep veins are incompetent

f Determination of Venous Pressure Venous pressure may be measured directly by introducing a needle into the vein and connecting it to an upright manometer The vein selected for the procedure must be placed at the same level as the right auricle if this is not possible or impractical corrections for the level difference must be made in reading the results Venous pressure is usually expressed in centimeters or millimeters of water the normal range being 60 to 160 mm [101 103]

Indirect mea urement of venous pressure can be done with the use of more elaborate instruments [104 10] On the other hand very simple bedside procedures[106] yield fairly good approximate values With the patient lying on his back the hand is lowered below the heart level to fill the veins on the back of the hand The hand is then gradually raised until the veins—being carefully watched—collapse The vertical distance reached between the dorsum of the hand and the level of the right auricle gives a good estimation of venous pressure

Venous pre sure can also be roughly estimated by observing the veins on the undersurface of the tongue These are normally collap ed when the subject is standing or sitting but are distended if the venous pressure is higher than 200 cm water [13]

g Venous Visuali ation The veins may be made to stand out and be visualized readily if a fluorescent substance is injected intravenously and the limb observed under wood light Exposing the limb to an infra red lamp will al o make the veins readily visible With infra red photography a picture of such veins may be taken

h Venography The venous system may be visualized radiographically As in contrast arteriography Diodrast is commonly employed The radiopaque substance may be introduced into the veins in a number of ways In indirect phlebography it is injected into the arterial trunk supplying the extremity roentgenograms are then taken at short intervals This method is theoretically the best but technical difficulties and sometimes unpleasant side effects are associated with it A simpler procedure is to inject the contrast substance into the venous system (direct phlebography) with a tourniquet applied to occlude venous return in the investigated extremity Because of the generalized distribution of the injected substance and despite the tourniquet visualization is sometimes poor Acute thrombophlebitis is a contraindication to phlebography

The contrast medium may also be introduced directly into dilated superficial or varicose veins The high concentration of the substance and the presence of venous stasis in the area make the ves els stand out beautifully

Varicose veins due to incompetence of the superficial set alone may be differentiated from those due to deep venous insufficiency by phlebography unless there is incompetency of the deep and communicating veins they cannot be visualized by injecting the contrast medium into the superficial varicosities [107]

SPECIALIZED METHODS OF MEASUREMENT

Some of the follwing tests and procedures which are designed to measure and document the behavior of the general circulation as well as the physiologic respon es of the circulation in the extremities are useful tools in investigative studies Since their performance requires the services of specially trained personnel and the u e of complex apparatus these procedures are rarely done in clinical practice Good clinical examination will suffice in most instances to arrive at a definitive opinion as to diagnosis and management

GENERAL CIRCULATION

a Cardiac Output Changes in cardiac output are necessarily reflected in the entire vascular tree Where there is impairment of arterial circulation as in obliterative vascular

partial or complete obstruction as a result of thrombophlebitis The resulting congestion may cause insufficiency of the valves of the communicating veins or the production of collateral channel Either condition may in turn cause superficial varicose veins that are grossly indistinguishable from the ordinary run of the mill variety which arise from congenitally defective valves

Various clinical procedures may be used to determine whether the varicosities were formed as a sequela of deep venous disease or if they are of the congenital variety The following tests are commonly used to evaluate the situation in cases of venous insufficiency

c *Modified Brodie Trendelenberg Test*[96, 97] With the patient lying on his back, the leg is elevated to empty the veins in the extremity The patient is then made to stand up and the veins are observed closely the examiner noting the rapidity of filling (filling time) as well as the direction of filling whether from above or below Normally the veins should fill slowly from below Filling from above indicates that the valves are incompetent Roughly slow filling from above—where the column of blood could be followed as it backflows into the previously emptied veins—signifies that only the superficial vessels are involved Rapid filling of the veins—where the source of backflow could not even be localized—indicates incompetence or insufficiency of the deep or communicating veins

The procedure is repeated and the veins emptied With the leg still elevated a rubber tourniquet is placed high around the thigh or pressure applied with the examiner's fingers to occlude the great saphenous vein as it empties into the femoral vein at the region of the fossa ovalis At the same time the small saphenous vein is occluded by digital pressure as the vessel drains into the popliteal vein in the popliteal fossa The patient is made to stand up with the applied pressures maintained If the varicose veins result from incompetence of the deep or communicating veins they fill despite the applied occlusion on the great and small saphenous veins If they remain empty then the defect involves either or both of the superficial segment The tourniquet placed high around the thigh (or the pressure applied on the great saphenous vein) is then released If the veins remain empty, the great saphenous vein is competent If they fill the great saphenous vein is the source of back flow If the veins remained empty even after removal of the tourniquet, but filled after removal of the pressure applied at the small saphenous vein only the latter vessel is incompetent

Filling of the veins upon releasing the pressure on the great saphenous vein necessitates a third performance of the procedure When the patient stands up the tourniquet is retained but the pressure on the small saphenous vein is released If the veins remain empty the incompetence is localized in the great saphenous vein, if they fill both the small and the great saphenous veins are incompetent

d *Perthes Test*[98] A rubber tourniquet is applied around the thigh with sufficient pressure to occlude circulation in the superficial veins The patient is then made to walk about the room If the dilated veins diminish in size, it indicates that the communicating and deep veins are able to compensate for the insufficiency of the superficial venous sets

e *Other Tourniquet Tests*[99, 100] Incompetent communicating veins may be localized by modifications of these tests The Trendelenberg test is done but after the veins have been emptied the tourniquet is applied at various levels of the thigh and leg before the patient is made to stand The defective vessel is indicated by the highest level where application of the tourniquet is followed by filling of the vein when the patient stands up The use of multiple tourniquets to prevent backflow from proximal superficial vessels or from other deep or communicating veins may yield even more specific information

In a modification of the Perthes Test (Mahorner and Ochsner) the tourniquet is applied at various levels of the thigh and leg and in each instance the effect of walking on the varicose veins is noted The effect of exercise or

ARTERIAL CIRCULATION

a Oscillometry and Oscillography[131-138] This method of examination is based on the principle that if optimum pressure (usually between 60 to 150 mm Hg) is applied through a cuff placed snugly around an extremity the pulsations of the underlying arteries are transmitted to the enclosed air in the cuff. By connecting the cuff to a delicate needle arrangement the pulsations are magnified and may be visualized as oscillations of the needle in front of a dial or recorded on a smoked drum or tracing paper. The amplitude of the observed oscillations has been taken as an index of the adequacy of the underlying large arteries. Hence diminished pulsations down to "zero reading" were interpreted as indicative of impaired and insufficient circulation suggesting the presence of arterial disease of either spastic or occlusive nature.

Erroneous interpretations of the results obtained with the procedure and its inadequacy to quantitate blood flow (due to the impossibility of calibrating the apparatus) have been pointed out repeatedly by various workers in the field. One can fully agree with the statement that the procedure is useful only for "recording pulsations in the extremities for future reference and for teaching purposes ... otherwise it is one of the least valuable of all methods of investigation of the peripheral circulation."[139]

The physical limitations of the procedure make it unable to indicate the presence or absence of circulatory insufficiency (which is best appreciated by the presenting of clinical manifestations) and unreliable as a measure of arterial blood flow. The anomalous course of even medium sized superficial arteries, the presence of thick subcutaneous pads in obese individuals and the presence of well developed but non pulsatile small arterial collaterals adequately compensating for totally or partially occluded primary arterial channels may render poor or absent oscillometric readings meaningless in the evaluation of the circulatory situation.

Sequential oscillography may however be useful in providing the examiner with visual evidence of the progress of occlusive vascular disease. It can also be useful in demonstrating the reopening of occluded originally primary arterial channels if this should occur in the course of therapy.

b Calorimetry[140-144] The circulation plays a considerable role in the regulation of body temperature. Vasodilatation of the surface vessels increases the vascular area exposed to the external environment promoting heat loss by radiation. Vasoconstriction does the opposite. Thus there appears to be a direct relationship between heat loss from a body surface and the vascular status in the same area. On the basis of this observation blood flow was estimated by measuring the heat loss of an extremity. This was done by immersing the extremities in water below skin temperature and calculating the heat loss from temperature changes observed in the water as measured from time to time.

There are a number of accepted objections to the method. The basic assumption that the blood is the only source of heat ignoring the fact that heat is generated for example by the muscular tissues is evidently erroneous. Furthermore the assumption that the average temperature of the water in the calorimeter may be taken as the temperature of the venous blood is acceptable only within narrow limitations.[144] Finally the temperature changes observed obviously reflect changes taking place in the blood only within superficial vessels (skin) while changes in the blood apportioned to the deeper tissues are hardly accounted for. There were moreover many technical difficulties involved in the method which made its use impractical and with the difficulty of interpreting its results it was discarded until recently revised by Mendlowitz[15] who modified the method without entirely eliminating the causes for objection.

c Surface Thermometry Based on similar deliberations as those that led to the calorimetric method, changes of surface temperature in various areas were observed, measured and

disease a decrea e in cardiac output may prove critical in producing arterial insufficiency and its sequelae On the other hand, some vascular disorders e g arteriovenous fistulae are capable of influencing cardiac output directly even to the extent of provoking heart failure

There are various methods to estimate cardiac output The principles involved the mathematical calculations required and descriptions of the methods are readily available in the literature [13 108 117]

b Circulation Time [118 122] The shortest time required for blood to flow from one point in the vascular tree to another is referred to as the circulation time of these points Having established normal values it is presumed that a prolonged or increased circulation time indicates a slow flow of blood while a shortened or decreased circulation time indicates a fast or short circuited flow of blood Using a systemic vein e g the antecubital vein as the starting point, an indicator substance may be injected intravenously and its presence detected at desired end points like the lungs and the tongue measuring respectively the arm to lung and the arm to tongue times In the first instance ether (0 25 ml) may be used the end point being indicated by the coughing reflex induced by the excretion of the drug in the lungs In the second instance decholin (3 5 ml of 20% solution) or saccharin (2 5 Gm in 4 ml of water) may be used the end point being indicated by the production of a bitter taste (or sweet taste) in the tongue The difference between the e two times is the lung to tongue time There are also methods[1 3 1] designed to measure pulmonary circulation time One of these is to introduce a radioactive substance (radium or Na 4) into an antecubital vein and to detect its arrival at the right auricle and at the brachial artery at the opposite side with a shielded Geiger Mueller counter The difference between the arm to arm time and the arm to heart time is a fairly good measure of pulmonary circulation time Another method is to use sodium cyanide where the drug (which acts in the carotid sinus stimulating respiration) is injected (0 25 to 0.5 ml of 2% solution) into the antecubital vein and the time recorded with a pneumograph and stop watch

The 'normal values vary a little with the different methods employed The arm to lung time (using ether) averages 6 seconds (3 to 8 seconds) The arm to tongue time (saccharin or decholin) averages 12 seconds (8 to 18 seconds) The arm to arm time (radio active substances) averages 7 seconds (2 to 14 seconds) The pulmonary circulation time (radio active substance or sodium cyanide) averages 11 seconds (7 to 14 seconds) With these values the speed of blood flow in the systemic and pulmonary circuits may be estimated

c Circulating Blood Volume Any change in circulating blood volume may influence peripheral blood flow and in turn be influenced by peripheral vascular disorders The various methods used are described in the literature [117 120 130]

d Blood Coagulation In certain vascular diseases where there appears to be some associated disturbance in the clotting mechanism of the blood (e g recurrent thrombophlebitis) studies of the various factors involved in blood coagulation are indicated By and large, such simple procedures as the determination of bleeding coagulation and clot retraction times are adequate for screening purposes Abnormalities in any of these values call for a more thorough hematologic work up and the performance of other tests including the determination of platelet count red cell fragility blood Ca Vit K plasma fibrinogen prothrombin time prothrombin consumption time platelet adhesiveness heparin tolerance plasma antithrombin activity and others

e Angiocardiography The intravenous injection of a radiopaque substance that permits the radiologic visualization of the individual cardiac chambers is very useful in the study of various congenital anomalies and valvular lesions of the heart which may be associated with congenital anomalies or secondary changes in the peripheral vessels

re ents the rapidity of arterial inflow per unit of time or the rate of blood flow into the part examined This rate is usually expressed as milliliters of blood per 100 milliliters of tissue (the volume of the enclo ed part divided by 100) per minute

The medium u ed within the syst m may be water or air The type de cribed above is based on air displacement If this method intended to evaluate blood flow to an extremity, is applied to a digit (finger or toe) or hand or foot the behavior of the circulation in the whole limb cannot be well judged because of the anatomical fact that the toes and fingers and hands and feet are (exception made of the bone) mostly kin with only very small muscle mass while the opposite is true for the rest of the extremity We have ascertained that the skin/muscle ratio is about 0 3—0 5 in the forearm and lower leg and 4—5 in the hand and feet [161] Results obtained with a large part plethysmograph [161] which permits the study of the whole foot foot and leg hand or forearm and hand are obviously more representative measures of blood flow to the extremity Furthermore because of the anatomical fact that (exception made to the bones) the hand and the foot are mo tly kin while the leg and forearm are mo tly muscle by determining blood flow in these large parts (blood flow to the leg is computed from the difference of the values derived for the foot and the foot and leg) the values obtained may be broken down to estimate separate skin and muscle flows in the extremity with more reasonable approximation As Allen, Barker and Hines point out the method i hardly applicable in ordinary clinical practice but we find it a mo t advantageous method for investigation of the physiology of the circulation and of the many methods now available doubtless the be t a the above mentioned authors have tated [139]

e Ergography [165 166] The u e of the ergometer and the ergograph (equipped with recording facilities) is ba ed on an attempt to tandardize the determination of claudication time as an index of blood flow to the mu cle bed of the extremity To test the upper extremities the patient is made to clench the hand again t a fixed resistance (provided by springs) keeping time with a metronome To test the lower extremities the patient is made to flex and extend the foot at the ankle either voluntarily (synchronous with a timing device) or by electrical stimulation Variation in re istance to exerci e is usually accomplished with springs or weights An electrically propelled treadmill or a physiologic bicycle has also been used for the purpose The time that elap ed from the beginning of exercise to the time when pain appears is noted as the claudication time On the ergograph the force (amplitude) and duration of muscular contraction may be recorded and claudication time as well as fatigue time graphically demonstrated

f Determination of the Oxygen Content of Peripheral Blood The amount of oxygen taken from the blood as it pa es through an extremity has been used to determine the adequacy of circulation to the extremity Oxygen consumption i determined from the difference in oxygen content of the arterial and venou bloods in the extremity (arteriovenous difference) [16] The u efulne s of the te t is limited by the fact that O saturation of the blood is influenced by various extravascular factors and the normal wide variation observed in venous oxygen saturation even under constant environmental and phy iologic conditions An oxymeter attached to the kin has been con tructed u ing color differences picked up by a photoelectric cell [163] The method is rather crude and hardly merits quantitation it also is dependent upon many nonvascular factors such as thickness texture and other qualities of the skin Since it is u ed in blu h areas many elements enter that bear no direct relationship to rate of blood flow An apparatus called the oxygen electrode [16J] eems to be much more promising Its use is till in the experimental tage however it can b u ed at varying depth and it appear to be by far the mo t accurate indicator of O consumption available at pre ent for tissues of the extremities

g Use of Radioactive Substances Sodium

used as indices of blood flow For this purpose various instruments and apparatuses have been devised including the Dermatherm [146] the potentiometer indicator [147] the Rubicon skin temperature measuring device [84] the electromotive thermometer [148] and the Dermalor [149]

By *and large there is a definite correlation* between a limb s surface temperature and its vascular status As mentioned previously vascular impairment as a rule is associated with coldne s of the part involved While isolated temperature readings may not give any definite information significant temperature differences between homologous parts of two extremities and in abrupt changes in those of *adjacent parts of the ame extremity are in*dicative of vascular disturbance Such differences may often be detected simply by the palpating hand without the u e of any apparatus and may even yield very useful information On the other hand the use of elaborate instruments to make the determination of temperature differences and changes may lead to erroneous conclusions if the value obtained are unqualifiedly taken as a measure of blood flow to the extremity As experience accumulates the limitations in interpreting surface thermometry as a mea urement of total blood flow to the extremity become more and more evident

The extreme lability of surface temperature in the upper extremities in line with the latter function of minute to minute adjustments to slighte t temperature changes in the internal and external environment on the one hand and the relative luggishne s of re pon e in the lower extremities (being called upon to react only in re ponse to gro s environmental temperature changes or to strong vasomotor stimuli) [150] on the other makes the interpretation of cutaneous temperature changes in either limb as reflecting total blood flow to the part rather questionable Furthermore while surface temperature *may logically be expected to* reflect changes in the vascular bed in the skin this does not necessarily mean that it likewise reflects (in magnitude or in direction) the circulatory status in the deeper vascular beds especially the muscles Finally sympathetic denervation of a limb fixes its surface temperature at a certain level (which persists for as long as regeneration of the severed nerves has not taken place) making the limb incapable of exhibiting changes in cutaneous tem*perature despite changes in blood flow in re*sponse to even powerful va omotor stimuli [151]

d Plethysmography If the rate of venous return flow to a limb or organ were to remain constant or if it can be momentarily suppressed, the character of arterial inflow to the part is reflected by changes in volume of the part Qualitatively an increase in volume of the part implies an increase in blood flow *to the part and a decrease in volume of the* part implies a decrease in blood flow Quantitatively the rate of blood flow (increase or decrease) may be determined by the rapidity or acutene s of this change in volume A number of plethysmographic methods[1 163] have been devised to measure blood flow all based on the above mentioned principles [164] In general the part to be evaluated is enclosed in an air tight and leakproof box or compartment which is connected through a nondi tensible tube directly to a recorder A train gauge or other electronic device may be interpo ed Changes in pre sure inside the plethysmograph box (cau ed by volume changes *of the part of* the limb in ide it) are then converted by the strain gauge into electrical impulses which are amplified and recorded in an attached direct writer by the induced excursions of a heated stylus Occlu ion of the venous return flow from the part is accomplished with a cuff applied around the part ju t proximal to the plethysmograph This cuff is connected to a pressure re ervoir with facilities for sudden inflation of the cuff to a pressure above venous pre ure but below diastolic arterial pressure If the change in volume of the extremity (following sudden venous occlu ion) as reg i tered by the excur ions of the recorder stylus is recorded on EKG or other suitable paper and run according to a et timing device the slope of the resulting curve (flow curve) rep

Changes in temperature of the external environment, like those of the internal environment produce vasomotor responses predominantly in the surface vessels Exposure to a cold environment causes constriction of the surface vessels diminishing heat loss and conserving body heat Exposure to a warm environment is followed by dilation of these vessels and heat loss

a Reflex Vasodilatation (Gibbon Landis Procedure) Vasodilator responses in the extremities may be observed and evaluated by exposing the body or reasonably large parts of it to heat or warmth[175-177] This or any experiment designed to test vasodilatation should be done against the background of mild vasoconstriction There are a number of procedures described in the literature but we have found the standardized method of Gibbon and Landis[178] most convenient and reliable We use this procedure The patient in a basal state lying comfortably on a bed is made to adapt to his environment in the constant temperature room maintained at 20 C (±0 5 C and 55% humidity The patient is considered adapted when the surface temperature at the plantar surface (glomus area) of the big toe has remained constant for at least 30 minutes as recorded quasi continuously by a Speedomax recorder An arm of the patient is then immersed up to beyond the bend of the elbow in a water bath maintained at 43 44 C for a period of about 45 minutes Vasomotor responses in the extremities are evaluated by periodic determinations of rate of blood flow measured with a large part venous occlusion plethysmograph

b Reflex Vasoconstriction[179] The opposite reaction is achieved if a part of the body is cooled instead of warmed This should be done against a background of mild vasodilatation For this purpose as in any type of experiment to test vasoconstriction the constant temperature room is kept at 25 26 C with the humidity at 55%

c Cold Pressor Test[180] The various factors that influence blood pressure are still largely unknown It seems however undisputed that the degree of peripheral vasoconstriction bears a relationship to systemic arterial pressure whether this is a function of general peripheral resistance of one or more specific vascular beds is under dispute

The effect of cold induced vasoconstriction on systemic blood pressure in man has been observed and used to determine vasomotor reactivity Baseline blood pressure readings are recorded then the subject s other hand is immersed beyond the wrist in water of 4 C for one minute while the blood pressure is recorded every 30 seconds After removal of the hand from the water blood pressure is recorded at 2 minute intervals The maximum rise of systolic and diastolic pressures is noted as also the length of time before basal readings are reached and the length of time it takes for the pressure to return to basal levels after immersion An increase of 20/15 mm Hg blood pressure a pre experimental period of 20 minutes and a post immersion period of 2 minutes are considered normal Values exceeding these figures are interpreted as an indication that the subject is a hyper reactor and that he has a hypersensitive vasomotor system The procedure is used more as a screening test to find potential hypertensives than to judge vasomotor reactivity in patients with peripheral vascular disease

d Cold Test This is a simple test where the patient immerses his hand in water *maintained at 15 C temperature If the test* is positive a urticarial or an angioneurotic edema like reaction occurs in the immersed part There may also be systemic manifestations which suggest a histamin like reaction Capillary micro copy reveals blurring or haziness of the outlines of the capillary loops due to the production of edema probably resulting from increased permeability of the capillary wall This procedure is a test for vascular hypersensitivity to cold rather than for vasomotor reactivity per se

3 Responsiveness to Pharmacologic Vasomotor Agents Various drugs have

and iodinated serum albumen have been used[170, 17] Both are excellent measures of blood volume in the part examined The interpretation of peripheral pick up with a Geiger counter or a scintillation tube in terms of blood flow however is rendered rather difficult by the diffusion factors and the physiologic shunting devices

TESTING OF VASOMOTOR RESPONSES

Under normal conditions vasomotor responses are elicited when the individual is exposed to vasomotive forces The nature or direction of the response is specific for any one stimulus although the magnitude may vary within certain limits in different individuals and within narrower limits in the same individual However this directional specificity may be said to exist only in certain vascular beds for other vascular beds in the body may not only not respond but may even exhibit the opposite reaction to the same stimulus at the same time such type of response in turn being specific for these other beds Thus if vasomotive stimuli physiologic as well as pharmacologic, are classified as vasodilator or vasoconstrictor it is most desirable that their action be specified in respect to the vascular bed or beds concerned Various physiologic states and many pharmacologic agents are referred to as peripheral vasodilators or peripheral vasoconstrictors because their occurrence or administration is followed by the respective vasomotor response in the blood vessels of the extremities However until better methods can be devised so that the blood flow in the vascular beds of the skin and muscles can be separated more accurately the additive effect of their responses have to be taken as the vasomotor response of the extremity as a whole On the basis of these facts certain physiologic states have been artificially induced and various pharmacologic agents have been administered to evaluate the vascular status of the extremity under the assumption that the vascular integrity is directly correlative to the normalcy (in degree and in direction) of the vasomotor response elicited

1 Responsiveness to Changes in Temperature of the Internal Environment Following profuse hemorrhage or other states characterized by loss of body heat a train of physiologic events sets in seemingly devised to conserve heat and to prevent further loss surface vasoconstriction takes place The consequent cold sensation has provided the term chill for the symptom complex representing the attempt to restore body temperature if the heat loss has been great On the other hand in febrile states where there is excessive production of body heat vasodilation of the surface vessels takes place increasing heat loss by radiation and convection Thus normally active vasomotion occurs at least in the surface vessels in response to changes in temperature of the internal environment Loss of responsiveness indicates disease of the vessels or disturbance in the regulatory mechanism

Injection of typhoid vaccine which was used in the treatment of thromboangiitis obliterans has been employed by the same workers[173, 174] to evaluate the vasomotor responses in the extremity The intravenous administration of 50 to 100 million dead or attenuated bacilli is followed by a sequence of events comprising (a) a latent period of about two hours and (b) a severe chill with rapid rise in body temperature reaching its maximum within 4 hours and subsiding gradually to normal The rise in skin temperature and increase in mouth temperature are noted as well as the difference between those two values (attributed to peripheral vasodilatation) These are used in a formula the Vasomotor Index (Brown) presumed to be an expression of the capability of the small peripheral vessels to dilate The index is obtained from the ratio of the difference between the two increases of temperature over the increase in blood (mouth) temperature a vasomotor index of 1 5 or more is taken to be indicative of good vasomotor responsiveness The unpleasant side effects and the dangers of the procedure have prevented its widespread use

2 Responsiveness to Changes in Temperature of the External Environment

be applied to differentiate between skin and muscle flow through simultaneous measurement.[179] Similar limitation and difficulties in interpretation apply as in thermometry. The procedure is perhaps better applicable to muscle flow than to skin flow since it measures oxygen consumption and there does exist a very definite relationship between work performance and muscle flow.

c. Plethysmography of large parts permits separate estimation of muscle flow and skin flow by using forearm or leg for estimation of muscle flow and hand or foot for estimation of skin flow.

The vascular bed of the skin is predominently concerned with heat regulation and therefore readily responds to changes in both the external and internal environment. These responses may be elicited directly as well as by central reflex and are almost entirely dependent upon the vasomotor innervation.[151, 190]

The vascular bed of the skeletal muscles. It has been shown by Grant[191] and his co-workers that in contrast to the skin bed vascular responses in the skeletal muscles were chiefly dependent upon the action of metabolites produced during activity. Barcroft and his co-workers[79] have ascertained that the vasomotor centre can regulate the basal flow in muscle but is unable to influence the circulatory changes during activity. This fact is unexplained as is the phenomenon of the sympathetic denervation of a limb increasing basal flow but depriving the limb of its capability to receive reflex increase in blood flow through body warming. These unexplained phenomena are most likely related. Barcroft and his associates even ponder the possibility that there may be two separate circulations in muscle, one controlled by the vasomotor centre and the other by metabolites.[79] Be that as it may, it is obvious that the responses of various vascular beds to vasomotor drugs must vary according to the regulatory mechanism active at the particular bed.

3. Relationships among Various Vascular Beds. The fact that vasomotor responses vary from bed to bed causes transposition of blood from one area to the other. This shifting of blood volume within the circulatory system is obviously a rather important factor in hemodynamics. Unfortunately information is still very incomplete and many a theory advanced over the years is still awaiting conclusive experimental and clinical confirmation. Probably the best way of gathering information on this problem complex is the one employed by Sharpey Shafer and his co-workers.[16, 4] They have studied the effect of such rapid methods of changing circulation as altering the posture, heating, cooling, exercise and the Valsalva maneuver. As far as the two main vascular beds in extremities are concerned, it appears most likely that shifting of blood from the skin to muscle and vice versa does occur. This seems to be most plausible when we consider the differences in apportioning of blood to the skin and muscle respectively in response to cooling, warming and exercise as well as the vasomotor phenomena connected with interruption of nervous regulatory mechanism.[79, 1, 1] The occurrence of shifting of blood between visceral and peripheral beds in man is far from proven. To some workers it appears to be an almost unavoidable postulate for explanation of certain features of shock and hypertension.

been used in the treatment of peripheral vascular disease because of their supposed vasodilator or vasospasmolytic properties. They are discussed in detail in Part IV. With each drug physiologic experiments conducted under well controlled conditions should be performed to demonstrate the alleged pharmacologic properties. When investigating vasomotor responses it is of paramount importance that the controlled conditions include basal conditions of the patient as well as the facilities of a regulatable constant temperature and humidity laboratory.

VASOMOTOR RESPONSES IN THE EXTREMITIES

1. Relationship to the Heart. The heart serves as the central pump that throws into the vascular system a given amount of blood at given intervals, at a given pressure, and with a given velocity. It is obvious that changes in the pumping mechanism must be reflected in the peripheral circulation and that such response becomes measurable whenever it reaches a magnitude sufficient to be documented by the limited methods available at present. Clinically, the response in the extremity beds to decrease in cardiac output may be found to manifest itself directly in two ways: in arterial constriction and in pooling of blood in the minute vessels. When cardiac output remains markedly diminished for a prolonged period of time, as in certain cases of tight mitral stenosis, the ensuing picture in the extremities might be almost indistinguishable from that of peripheral arterial insufficiency due to intrinsic occlusive peripheral arterial disease. This includes even such extreme manifestations as marked trophic changes and gangrene, both of which may occur without the presence of a ball valve thrombus.[181, 182]

Conversely, marked changes in the distribution of blood volume within the peripheral vascular system must necessarily affect the mechanics of the heart.[183, 184]

2. The Vascular Beds within the Extremity. There are at least three distinct vascular beds in the extremity, namely, in the bones, the skeletal muscle, and the skin. The vascular supply to the connective tissue found between the individual muscle bellies and separating skin from muscle in certain places seems of minor if any significance. Vascular supply to soft tissue structures in and around the joints is of great interest, but there is no method available to measure blood flow to these structures in man. Blood flow to the bones may be measured;[185] however, the method is cumbersome and has not proven rewarding so far.

There are three main reasons for separating skin flow from muscle flow: (1) The impact of vascular disease may be equal on the two beds, but more often is found to be predominantly on one of them at the time. (2) The regulatory mechanisms chiefly responsible differ in the two beds: skin flow is to the greatest part regulated by sympathetic innervation, while rate of muscle flow mostly depends on the circulation and transport of metabolites in work performance. (3) The respective responses of the two beds to the same stimulus may differ quantitatively or even directionally.

There are at present three methods available that permit an approximate separate estimation of muscle flow and skin flow in human extremities.

a. Thermometry, using simultaneously thermocouples inserted into muscle bellies and thermocouples affixed to the surface of the limb. Registration of surface temperature is an indication of blood flow through the skin only under certain circumstances.[186, 187] Local effects of insertion of the thermocouple and the fact that merely local temperature is measured in a few places render conclusions concerning blood flow to the whole muscular bed of the part difficult.[188] Basically, thermometry seems better applicable to the skin bed than to the muscle bed, since heat regulation is the outstanding physiologic function of skin flow.[189]

b. The use of the oxygen electrode may

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Part II Pathologic Alterations in Peripheral Blood Flow

CAUSES FOR ALTERATION in peripheral blood flow are of course manifold Most changes represent physiologic responses to various needs arising within the body s economy in the fulfillment of life s daily requirements

Changes in peripheral blood flow due to pathologic interference may be conveniently divided into two main groups alterations caused by and representing sequelae of intrinsic disease of the blood vessels and alterations representating response to and sequelae of pathologic processes outside the vascular system

Pathologic processes affecting blood flow *may manifest themselves predominantly in* one or more of the three main segments of the vascular tree producing the sequelae of interference with the inherent function of the affected segment Thus pathologic processes affecting the arterial segment cause diminished or inhibited supply of arterial blood to the part leading to privation in nutrients and oxygen this in turn causes pain pallor change in surface temperature and trophic changes Tissue necrosis (usually called gangrene when the extremities are concerned) ensues when ever the arterial blood supply to the part is markedly impaired or totally obstructed

When the venous part of the circulation is affected drainage of blood from the part is impaired This leads to stagnation of blood and accumulation of waste products including CO causing in turn discoloration changes in surface temperature swelling pitting edema and pain

Finally interference with proper function of the minute circulation affects metabolic exchange through the capillary wall and may lead to increased capillary permeability local *edema diminution or loss of capillary response* to stimuli (usually referred to as loss of capillary tonus) hemorrhage and even necrosis

Alterations in blood flow may be acute or chronic reversible or irreversible Obviously where such alterations result from extravascular pathologic processes all parts of the vascular tree may be affected at the same time Moreover even in the case of intrinsic vascu

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thrombus forms locally on the basis of the atheromatous ulcer in the vessel wall and at a certain moment occludes the vessel lumen Very frequently atheromatosis occurs in combination with obliterative arteriosclerosis a disease to be discussed later Likewise atherosclerosis is frequently superimposed upon obliterative thromboangiitis (usually called Buerger's Disease) Acute thrombotic arterial occlusion may also occur following an acute inflammatory process in the arterial wall

Primary acute arteritis is a rare condition but does occur especially in children Two of the cases reported by Kramer[35] were observed in boys and a third in an elderly woman In these cases the condition appeared as a generalized arteritis All the arteries both large and small were involved although the medium size and smaller arteries showed the greater changes Pathologically there were swelling and proliferative changes in the intima with necrosis in some area In other areas thrombi were found on the intima with complete obliteration of the lumen in some vessel The media was frequently involved with infiltration of all types of cell followed by hyaline degeneration and fibrosis There was also cellular infiltration in the adventitia and in the perivascular tissues The symptomatology is essentially that of an acute infectious process with a clinical picture of a severe toxemic state with a sudden onset remittent fever rapid pulse headache malaise vomiting generalized pains and pains in the extremities of varying intensity Purpuric hemorrhages may be seen on the body or more prominently in the extremities especially in the lower limbs There may be gangrenous areas of varying sizes depending on the caliber of the arteries involved When the larger trunks are involved the impairment of the peripheral circulation is quite evident, with loss of the pulse coldness of the extremity discoloration and ultimate extensive gangrene There is leukocytosis with polynucleosis platelet count bleeding and clotting time remain normal

Secondary acute arteritis may occur for instance when the vessel traverses an abscess cavity the outer part of the vessel wall seems to have a marked resistance to bacterial invasion which accounts for the relatively rare incidence of such event When it occurs it starts as a periarteritis with polymorphonuclear leukocytic infiltration of the entire vessel wall and destruction of the elastic lamina which in turn may result in severe or fatal hemorrhage

Acute endarteritis following lodgment of a septic embolus from a septic thrombus or from the vegetation of an acute or subacute endocarditis may also lead to acute arteritis with inflammation and infiltration of the whole arterial wall the resultant secondary thinning causes the formation of a mycotic aneurysm or rupture of the vessel

Acute arteritis may also occur *secondary to generalized infections and inflammatory processes* Diseases that have been mentioned as involving arteries with subsequent development of gangrene include typhus fever[36] influenza diphtheria[3] streptococcic sore throat, erysipelas[39] anthrax gonococcal infections[39] malaria[40] and rheumatic fever[41-44] The symptomatology is necessarily dominated by the primary disease the vascular involvement presents a complication either in the acute clinical stage or during convalescence Symptomatology referable to the arterial complication depends upon the site of involvement and varies in severity according to the completeness of vascular occlusion ranging from tingling and numbness to actual pain with blanching coldness discoloration and gangrene of the part.

Subacute non pyogenic arteritis has been reported as a complication of typhoid fever and septicemia (bacterial emboli)[45] pneumonia and scarlet fever (due to toxic capillary injury)[46] and other general infection The lower extremity vessels are mostly involved

Rheumatic arteritis is a well described morphologic entity involving the small arteries the *arterioles and the capillaries*[47] and has been reported to involve a variety of such peripheral vessels as the cerebral pulmonary cor

lar diseases, in many instances should the disturbance *last for a prolonged period of time,* all segments ultimately participate to some degree Various types of pathologic processes affecting peripheral blood flow have of course, various organs as sites of predilection Discussion presented here will predominantly consider blood flow to the extremities

Chapter 1 Acute Intrinsic Vascular Disorders

ARTERIAL SEGMENT

Acute arterial occlusion is the term used for those incidents in which the main arterial supply to the part appears to be cut off rather suddenly Symptomatology may be instantaneous but more often develops within minutes to an hour In the extremities the presenting symptoms are coldness (subjective and objective) pallor and numbness The pallor soon gives way to a mottled cadaverous appear*ance and the numbness to intense pain,* the affected part of the limb becomes extremely sensitive even to light touch

Acute occlusion in the arterial tree may be caused by an embolus or by local thrombus formation Differentiation is often difficult but should always be attempted because of essential differences* in management The presenting symptomatology is identical Suddenness of onset is not of great help since in many case only the complete thrombotic occlusion *with its dramatic sequelae makes the patient* and his surroundings aware of the pathology while the preceding slow development of such pathology may be entirely overlooked or misinterpreted There is a striking similarity of events to those encountered in many cases of myocardial infarction due to thrombotic coronary artery occlusion

The best lead to a decision whether acute occlusion of an extremity artery is thrombotic or embolic in nature is the evaluation of the *patient* as an individual case The presence of heart disease especially of rheumatic etiology in the absence of peripheral manifestations of vascular disease speaks strongly for embolic and against *thrombotic occlusion* and vice versa Meticulous search into the history is of great importance Blood dyscrasias diseases leading to cachexia malnutrition are factors to be considered in the development of mycotic thrombi in peripheral arteries however this is extremely rare except in the presence of acute or subacute bacterial endocarditis[1 2]

Atherosclerosis* is by far the most frequent etiologic factor responsible for acute thrombotic occlusion of peripheral arteries[3] A

* Atherosclerosis or atheromatosis as it used to be called is characterized by a fatty change and fibrous thickening of the intima of the larger arterial vessels With the more effective control of infectious disease and the resultant lengthening of the population s life span there is an apparent increase in the incidence of degenerative diseases" Thus atherosclerosis and arteriosclerosis which had heretofore been looked upon as barely more than stigmata of aging are being considered more and more for their *pathogenic potentialities Because of their relative irreversibility once established they represent perhaps the most potent threat to that lengthened life* Consequently atherosclerosis and arteriosclerosis have become the subject of intensive investigation while much information has been gathered, their pathogenesis is far from understood This book is hardly the place to review these studies Two discrepant hypotheses regarding etiology might be mentioned *The most widely accepted "diet hypothesis*[3 31] proposes that due to a disorder of fat metabolism an excess of lipid material occurs in the blood stream which in turn leads to fatty deposits in the arterial wall The presence of such lipid deposits induces reactive overgrowth of connective tissue resulting in fibrous thickening of the arterial intima On the other hand proponents of the "thrombus" hypothesis think that sclerotic lesions are altered thrombi mural *thrombosis is believed to be possibly the consequence* of some abnormality in the various factors related to blood coagulation[3 34] According to this concept a mural thrombus that has formed in the vessel wall becomes covered with endothelium and thus becomes incorporated into the vessel wall and with subsequent organization fatty changes occur which might lead to softening ulceration and even calcification

established Attempts to differentiate phlebothrombosis from thrombophlebitis[83] at least clinically are unrewarding if not impossible The mechanism of intravascular coagulation is not clearly understood For a discussion of the subject and review of the literature, the work of Welch[84] and Nygaard[85] should be referred to Various factors are known to influence or to play a part in its production but the extent of their respective roles is unknown Among them are injury to the vessel wall,[61 6] obstruction or slowing of the blood stream[78] change in viscosity and composition of the blood (e g albumin content)[79] and changes in the coagulative properties of the blood[0 8]

Damage to the venous wall may be due to intrinsic disease (especially phlebosclerosis) or it may be of infectious (e g pneumonia influenza typhoid fever) traumatic (e g., following intravenous instrumentation) mechanical chemical (perivenous infiltration) or tumor metastatic origin[9 88] It may also be produced by direct extension from local suppurative foci as in puerperal sepsis mastoiditis and osteomyelitis

Changes in coagulative properties of the blood occur under various circumstances for largely unknown reasons and their role in thrombus formation is not too well established Acceleration in the prothrombin activation mechanism has been found to occur in postoperative and postpartum states[9 9] and this defect in the clotting mechanism has been assumed to be one of the reasons for the frequent occurrence of thrombo embolic complications after childbirth and major surgery

Slowing of the blood flow seems to have a rather striking relationship to thrombus formation Three very common conditions frequently associated with intravascular thrombosis might be mentioned here 1 Slowing of the systemic blood flow associated with congestive heart failure particularly in mitral stenosis or following myocardial infarction[93 9] as well as that consequent to sudden drops in arterial pressure 2 Local impediment to blood drainage resulting for example from pressure upon the femoral vessels by a pregnant uterus or a pack of enlarged lymph glands[96-98] 3 Prolonged bed rest especially in obese and elderly individuals is frequently associated with venous thrombosis[100 10]

Superficial thrombophlebitis involving the saphenae system producing a visible and palpable painful cord offers no diagnostic problem and is as a rule of little significance However it may be of diagnostic import in the history of obliterative thromboangiitis

Deep venous thrombosis is a bothersome often painful condition with a tendency to recurrence and to establishment of chronic sequelae Its most serious aspect however is the occurrence of embolism An estimated 80 to 90% of thromboses occur in the lower extremities most of them in the calf veins[103] The diagnosis of deep venous thrombosis is based on the described circumstantial evidence and the signs and symptoms due to impaired venous drainage deep muscle tenderness painful hot red and indurated overlying skin A positive Homans sign (pain on dorsiflexion of the foot) is helpful in establishing the diagnosis while a negative test does not exclude it by any means As is to be expected most embolic episodes arising from thrombi in systemic veins occur in the lungs Paradoxical embolism to the brain or to the extremities may occur in the presence of a patent foramen ovale A patient who either has manifest peripheral venous thrombosis or in whom one or more of the predisposing factors are present should be suspected of a pulmonary embolism in the occurrence of a sudden increased heart rate with or without rise in temperature Cough is usually an early sign hemoptysis may or may not follow Pain that accompanies pleural involvement by the pulmonary infarct is especially marked in basal lesions Fever and secondary pneumonitis often appear two or three days later Massive pulmonary embolism may cause sudden death or be followed by the signs and symptoms of acute pulmonary heart disease Subacute cases may present as congestive heart failure a very small embolism may be easily overlooked

onary and mesenteric arteries[42] as well as those of the kidneys, ovaries testes and the perirenal and periadrenal fat[43] It is described as a panarteritis with occasional secondary thrombosis[48] Rheumatic arteritis is characterized by inflammatory lesions resembling those of the pericardium and endocardium with marked reparative processes and early vascularization of the thickened intima so that complete occlusion of the vessel never occurs[47] despite the rather extensive involvement of the vessel wall Kramer and Bayliss[44] demonstrated severe exudation and necrotizing arteritis in rheumatic fever and suggested that severe myocardial damage may result from the circulatory disturbances caused by these lesions In active cases the involved vessels show proliferation of the fibrous and elastic tissue similar to that of arteriosclerosis Oddly enough there have been no reports of rheumatic arteritis of the extremities nor have there been reports of a nosologic entity attributable to rheumatic lesions in this part of the vascular tree

Traumatic causes of acute arterial occlusion include pressure from cervical ribs crutches fracture etc and other injuries of the extremities[49]

Thrombotic Microangiopathy or thrombotic thrombocytopenic purpura is an acute thrombotic vascular disease characterized by partial or complete occlusion of numerous arterioles by hyaline or granular thrombi with a certain amount of endothelial reaction and absence of inflammatory cellular infiltration Clinically its manifestations include acute hemolytic anemia thrombocytopenic purpura fever and ill defined neurologic disturbances The etiology is unknown The thrombocytopenia and occlusion of vessels are generally held to be due to formation of platelet thrombi but the pathogenesis is not understood Cases reported in the literature have been uniformly fatal[53 6]

Acquired (traumatic) arteriovenous fistulae are mentioned here as a form of acute peripheral arterial disturbances because the acutely established arteriovenous shunt if large enough causes considerable repercussions in the general circulation

The most common causes of the condition are gunshot or penetrating wounds from other causes and the vessels most frequently involved are the femoral brachial and carotid arteries Locally, the affected limb shows venous engorgement increase of surface temperature and sometimes edema Peripheral ischemic symptoms may predominate and the toes may be unduly cold or even gangrenous A machinery murmur and/or thrill are elicited over the lesion[45] The blood flow in the affected limb is variable apparently reduced in recent cases but increased in old ones, while the blood flow in the unaffected limbs remains normal The effect on the general circulation is manifested by tachycardia, elevation of venous pressure increased pulse pressure increased total blood volume increased stroke volume and cardiac output and ultimately cardiac enlargement If the shunt is large enough symptoms of congestive heart failure (high output failure) may eventually develop If the shunt is *temporarily obliterated by digital pressure over the lesion* the pulse rate falls (Nicoladoni Branham sign) the blood pressure rises the venous pressure falls slightly and the cardiac output decreases with accentuation of capillary pulsation[49 5 61 63]

VENOUS SEGMENT ACUTE PHLEBITIS AND VENOUS THROMBOSIS

Inflammation of peripheral veins as a disease entity occurs in the course of various often minor infections It is characterized by tenderness redness pain swelling and increased warmth of the part Inflammation of the vein *or phlebitis usually recedes within 24 to 48* hours However it may persist for several days and when it does it is invariably because of an associated thrombus formation producing the entity known as thrombophlebitis The occurrence of phlebothrombosis or intravascular thrombus without any primary or secondary inflammatory changes in the vessel wall as a clearly defined clinical entity has not been

the atheromatous plaques undergo hyaline changes and necrosis with calcium deposition and even bone formation In both conditions the intima is the site of maximum involvement and medial changes when present are minimal and believed to be secondary This is seen mostly in the aorta and larger vessels and smaller arteries including the coronary cerebral and renal arteries Arteriolosclerosis‡ is characterized by subintimal hyaline thickening and narrowing of the lumen with subsequent involvement of the muscularis This is seen to affect the arterioles (arteries of 100 micra or less in diameter) of the kidneys pancreas spleen and adrenals Renal arteriolosclerosis of which there are two subtypes is seen almost exclusively in hypertension One associated with benign hypertension is characterized by subintimal hyaline degeneration and elastosis or elastic hyperplasia and the other seen in malignant hypertension is characterized by intimal hyperplasia* with cellular and subsequent fibrous narrowing of the lumen and arteriolar necrosis† involving the whole thickness of the vessel wall

In their pure form these various types of arteriosclerosis appear to be distinct from one another in etiology pathology and clinical manifestations However while such pure forms do occur the two major types characterized by evenutal calcification—Moenckeberg s sclerosis and atherosclerosis—very frequently occur together especially in the aged although the extent of one process may have no connection whatsoever with the severity of the other Whether metabolic or humoral factors or their disturbances may be the cause or in some way influence the production of both or either and whether the presence and extent of both or either may be demonstrable clinically by chemical or physiochemical methods still awaits elucidation

Obliterative arteriosclerosis‡ a manifestation of generalized arteriosclerosis is the most frequent cause of chronic often progressive peripheral arterial insufficiency, involving primarily the medium sized arteries especially those of the lower extremities It affects the male population five to six times more frequently than the female [1 8 179] and occurs in increasing frequency with age especially after the fifth decade [130] Its incidence in the female population however increases considerably after the menopause Diabetes mellitus predisposes to the occurrence of the disease in the former s presence the latter runs a more fulminant course [131 135]

Histopathologically obliterative arteriosclerosis is characterized by medial sclerosis (Moenckeberg s arteriosclerosis) with varying degrees of intimal thickening as a result of superimposed atheromatosis or atherosclerosis Herbut[1 7] describes the arterial changes as predominantly of a fibrous nature with only small deposits of fat but with frequent vacuolization and calcification It would appear then that the clinical manifestations of the disease depend on the degree of circulatory impairment caused by the intimal thickening and possible intravascular thrombosis and the consequent obliteration of the arterial lumen However two facts must be mentioned here First an atherosclerotic plaque may be more damaging in some locations compared to other and second the ability of the body to develop collaterals may provide adequate blood supply to body parts whose primary circulation is completely obliterated by the sclerotic process while on the other hand symptoms may occur even when the primary circulation is not as badly impaired if adequate secondary circulation fails to develop

Clinically then obliterative arteriosclerosis as a disease entity implies interference with arterial circulation to a degree to be appreciable subjectively (intermittent claudication rest pain) or objectively (disappearance or diminution of peripheral pulses coldness of the extremity postural color changes muscular atro

‡ Syn diffuse arteriolar sclerosis diffuse hyperplastic sclerosis

* Syn productive endarteritis, hyperplastic arteriolosclerosis endarteritis fibrosa

† Syn arteriolonecrosis necrotizing arteriolitis

‡ Syn arteriosclerosis obliterans

MINUTE VESSELS

Exanthemata and enanthemata observed in various acute infections are clinical expressions of involvement of the minute blood vessels in these diseases This might be brought about by toxic injury to the capillary wall (scarlet fever)[46] with necrotizing lesions (smallpox)[108] or through bacterial embolization (meningococcemia, septicemia typhoid)[11, 4, 105] The type of involvement of the minute circulation in entirely reversible exanthemata has not been clarified as yet despite many interesting observations There has been no satisfactory explanation for the peculiar and characteristic distribution of the exanthemata in the various eruptive fevers nor for the predilection for the skin capillaries over those of the mucous membranes in some diseases and their equal involvement in others[106-108]

Little is known about the behavior of minute vessels in the parenchymatous organs[109, 111] except perhaps the kidneys

Acute burns permit only an indirect study of capillary regeneration in the course of skin grafting[11] Acute cold injury either at freezing (frostbite) or subfreezing (trench foot immersion foot) temperatures has been studied extensively[113, 124]

Chapter 2 Chronic Intrinsic Vascular Disorders

ARTERIAL SEGMENT

Any of the acute conditions discussed in the preceding chapter can become chronic whereby either restitution or ultimate sequelae are delayed and symptomatology persists for an indefinite time this varying widely from case to case

In addition there are conditions of the arterial system that are characterized by an insidious onset and a chronic course which may or may not be interrupted by acute bouts

Arteriosclerosis For all the current interest in arteriosclerosis and atherosclerosis and the tremendous amount of intensive research being conducted to understand the etiology and pathogenesis of these conditions there is not much to show to negate Clifford Allbutt s remarks concerning causes of arteriosclerosis to the effect that our path is cumbered with guesses presumptions and conjectures[1, 5] To enumerate let alone discuss the various theories and hypotheses would be beyond the scope of this book suffice it to say that current concepts tend to implicate primarily some disturbance in cholesterol (lipid) lipoprotein metabolism Pathologically however there is much in agreement and a brief review of the various terms and what they signify would be in order[47, 1, 6, 127] Arteriosclerosis is a generic term that, freely translated means loss of elasticity thickening and hardening of the arteries Obviously this description is on the gross pathology level and would be applicable to any of the various conditions of the arteries where such physical properties are demonstrable Such conditions in turn are differentiated from each other histopathologically Moenckeberg s sclerosis * considered to be essentially a senile change is characterized by degeneration of elastic tissue and fibrosis of the smooth muscle in the tunica media followed by calcification producing the gooseneck or pipestem arteries due to localized and sometimes encircling calcium plaque along the course of the vessel The intima may show no change or may show a moderate degree of thickening without however materially interfering with the circulation This may occur in all arteries including the aorta but is most frequent in the arteries of the extremities Atheromatosis refers to a condition of the artery characterized by newly formed connective tissue and focal yellowish thickenings or deposits in the intima composed of gruellike or pultaceous lipoid material *Atherosclerosis*† is a more advanced state where

* Syn senile arteriosclerosis media sclerosis medial calcinosis

† Syn nodular sclerosis

large arteries and veins may have their share in the late stages of the disease Because of the extensive inflammatory process involving the vessels and the perivascular tissue it is not unusual to see the artery vein and nerves bound together by fibrous tissue on biopsy in cases of long standing

The disease affects men predominantly mostly in early adult life The deep arteries and veins of the legs are the ones usually involved although those of the upper extremities and other vessels in the body may be involved especially in severe cases[14 1 1] In about 40% of the cases there is also early involvement of the superficial veins seen clinically as painful red spots or streaks and lasting from one to several weeks with frequent recurrences this has been termed superficial migrating phlebitis

As is so commonly seen in slowly developing conditions the patient often does not complain of any symptoms attributable to the early stages of the disease except in the instances of superficial migrating phlebitis The really troublesome symptoms occur late in the disease and are invariably the consequence of arterial insufficiency due to marked impairment of the primary channels or to disturbances in the secondary or collateral vessels or both

Clinically thromboangiitis obliterans is very frequently confused with obliterative arteriosclerosis A differential diagnosis between the two conditions is therefore necessary (See Table I)

Cases of thromboangiitis obliterans and obliterative arteriosclerosis have been called from time to time endarteritis obliterans However with the more extensive morphologic studies of these conditions the practice has been gradually abandoned

Obliterative Endarteritis Semantically this designation connotes an inflammatory process involving medium sized or small arteries with occlusion or narrowing of the lumen of the vessel The inadequacy of the term to denote a specific nosologic entity becomes evident immediately As Boyd points out the term although in common use is not a desirable one It is apt to give the impression that it represents a definite disease entity which is certainly not the case And furthermore nor is the process an inflammatory one but rather productive in type

The various conditions where it is said to occur include[47] certain physiologic states such as (1) obliterating connective tissue proliferation of the intima seen in the umbilical and hypogastric vessels and the ductus arteriosus in the child soon after birth (2) that seen in the vessels of the sexual organs in old age and (3) that observed in the uterine vessels after parturition Disease states where it occurs include (1) the intimal thickening seen in vessels in the neighborhood of any form of chronic inflammation as for instance in the base of a gastric ulcer (2) syphilis where it is supposed to arise from active periarteritis caused by the spirochaetes[1] (3) cavernous tuberculosis of the lungs where extensive thrombosis usually change vessels into almost solid cords (4) Ayerza's disease where there is marked thickening of the intima with narrowing of the lumen of the small arteries and arterioles in the lungs concomittant with dilatation and sclerosis of the main branches of the pulmonary artery associated with pulmonary hypertension and (5) ergotism It is interesting to note that advanced vascular changes produced experimentally in the rat's tail by sacral injections of ergotamine are indistinguishable morphologically from those seen in thromboangiitis obliterans in man[1 3] It may be only a matter of time when as in the cases of TAO and OAS better and more definitive studies of these conditions will develop a more appropriate term for each of them and the term endarteritis obliterans having outlived its usefulness will be relegated to the pages of history

Another interesting entity that might be mentioned here is *Temporal Arteritis* This condition was first described by Hutchinson and later more clearly by Horton Magath and Brown[1 1 6] who suggested its term designation Subsequent case reports however especially of severe fatal ones have shown that

phy trophic changes in the skin and its appendages ulceration and gangrene) It might indeed be well to refer to this clinical symptom complex as sclerotic peripheral arterial insufficiency instead of obliterative arteriosclerosis, which neither describes accurately the pathologic changes nor suggests whether or not clinical signs or symptoms may be expected

In most cases it is possible to ascertain other evidence of arteriosclerosis or atherosclerosis, such as aortic sclerosis arteriosclerotic heart disease coronary disease cerebral arteriosclerosis or nephrosclerosis Since arteriosclerosis is usually well advanced when it involves the cerebral arteries the retinal arteries which constitute a part of the cerebral bed may possibly provide a clue to the status of the vascular tree as a whole

While pathologically, obliterative arteriosclerosis is usually bilateral the non uniformity of the degree of atherosclerosis and the inconstant occurrence of atheromatous thrombotic occlusion with its sequelae may cause the manifestations of arterial insufficiency to be evident only on one side to the total exclusion of the other

Thromboangiitis Obliterans * This is the next most frequent cause of peripheral arterial insufficiency Samuel s review of this disease s history —which has been observed for centuries—serves as a detailed reference [136] The first indication that the disease was recognized as a separate and distinct entity may be ascribed to Balling who in 1830 alluded to a juvenile type of gangrene [13] In a report on his study of spontaneous gangrene in 1872 Leffas advocated a conservative treatment of the condition [138] An inflammatory process in the arteries with involvements of the intima and subsequent thrombosis and obstruction was described in 1876 by Quincke [139] In that same year Friedlaender used the term Arteritis Obliterans to refer to an inflammatory lesion of the pulmonary vessels [140] It remained for Von Winiwarter in 1879 to make the first detailed description and illustration of the arterial and venous changes in the leg of a 57 year old man who had an amputation after a 12 year symptomatology a condition Von Winiwarter called endarteritis and endophlebitis of the leg Such changes are characteristic of the condition we now call thromboangiitis obliterans [141] Many reports in the early literature that appeared subsequently seemed to deal with thromboangiitis obliterans In 1908 Eising [14] in a case reported before the New York Pathological Society, directed attention to the aggravating influence of smoking on the disease [143] In 1908 Buerger s first paper on the pathology of the disease was published [144] suggesting the use of the term thrombo angiitis obliterans and in 1909 Parkes Weber, in England reported similar studies [145]

In his book [146] Buerger described in minute detail the gross and microscopic findings in the disease as well as its various pathologic and clinical stages and he discussed his concept of its pathogenesis Since these classic descriptions thrombo angiitis obliterans' has been established as a definite clinical entity often called Buerger s Disease in recognition of that scientist s excellent contribution to its pathologic identification

As Buerger pointed out the essential lesion was not a degenerative process but an inflammation of the vessel wall with consequent thrombosis involving both arteries and vein The lesion occur segmentally with the thrombus occluding the vessel completely in some part with intervening normal portions which are free from lesion of any detectable degree Absence of suppuration and necrosis is characteristic The intensive organization of the thrombus and subsequent fibrosis with the canalization that may occur to some degree might give the impression of a thickened intima in the cut section A more critical examination of the lesions with the use of elastic tissue fat and calcium stains however easily determines the true nature of the obliterative process In any event calcification in involved vessels in elderly subjects does not rule out the disease since superimposed arteriosclerosis is very frequent in these cases The medium sized and small vessels are the ones chiefly involved but the

* Syn Buerger s Disease Presenile gangrene

from the artery to its accompanying vein through an abnormal opening or channel without passing the capillary bed. It may be congenital or acquired. The congenital type is usually multiple and results from failure of the vessels to differentiate and separate completely during their embryonic development from a common anlage. This may occur in any part of the body but is most frequently seen in the extremities. Presumably due to increased circulation in the involved extremities there is increased growth of the limb including the bones and not infrequently it is out of proportion not only to its opposite member but to the rest of the body as well. This condition produces what is known as giant limbs. Increased growth of hair and undue warmth of the part are commonly observed. Varicose veins are present as a rule and their presence in early life may serve as a lead to the diagnosis of the condition. Ulceration and gangrene may occur as a complication of the condition presumably attributable to chronic venous stasis and to relative arterial insufficiency due to shunting of blood away from parts distal to the lesion.

As mentioned earlier acquired arteriovenous fistulae are traumatic in origin. When sufficiently large vessels are involved normal hemodynamics are interfered with rather abruptly; the repercussions in the cardiovascular system are dramatic and may be of serious nature. If the acquired shunt is not corrected and the patient survives the acute stage with its immediate complications the circulation ultimately adjusts to it and there ensues a chronic compensated state where the pathophysiologic effects of the vascular short circuit are present to a degree dependent on the size of the defect. These effects may be easily demonstrated. In our discussion we shall limit ourselves to arteriovenous fistulae occurring in the extremities.

The involved extremity increases in size and length (if the fistulae were acquired before the closure of the epiphysis). Extensive venous varicosities may be well visible or easily palpable. There may be some degree of edema and increased pigmentation as well as increased hairiness of the limb. There is increased warmth of the part. Thrill and bruit are easily detected over the lesion. Due to the resulting venous insufficiency stasis ulcers are not uncommon complications.

The effects of a sufficiently large arteriovenous shunt upon hemodynamics are manifested by an augmented venous return and elevated venous pressure, increase of blood volume and cardiac output and subsequent dilation and hypertrophy of the heart which might eventually lead to high output failure with the symptomatology described above. Diagnosis of the condition is established by the history of the original injury, the above physical findings, arteriography and by the fact that oxygen saturation of venous blood taken from the involved limb is considerably higher when compared to that taken from the normal side.

The so called collagen or fibrinoid diseases must be mentioned here because of the distinct and pathognomonic vascular lesions seen in some of the diseases of this group. *Polyarteritis nodosa** [173, 17] is considered to be a primary vascular disease occurring frequently in males especially during the third and fourth decades. There is fibrinoid degeneration involving medium sized and small vessels as well as capillaries. Irregularly disposed segmental fibrinoid necrosis of the media associated with leukocytic and eosinophilic infiltration of the vessel wall is the basic pathologic picture. There is subsequent involvement of the other vascular coats with intravascular thrombosis, recanalization, aneurysm formation, granulation and fibrosis with healing taking place by scar tissue formation. Vessels throughout the body may be involved and the presenting clinical picture depends upon the organ or organ system most affected at the time. Involvement of the arteries of the extremities presents with symptoms of arterial insufficiency, joint and muscle pains. Cutaneous manifestations may include subcutaneous nod

* Syn periarteritis nodosa, polyangiitis, panarteritis, necrotizing angiitis

Table I

	Thromboangiitis Obliterans	Obliterative Arteriosclerosis
1 Age and onset of symptoms	Young adult life 20 40 years	Usually over 50 years may also occur however in young adults especially diabetics
2 Sex	Predominantly in males	Predominantly in males in younger age groups At past 60 occurrence in females not unusual especially in the presence of diabetes mellitus
3 Site of involvement	First lower extremities Upper extremities may be involved in advanced and severe forms of the disease Small and medium sized vessels usually involved Large arteries or veins involved only in advanced cases	Almost exclusively the arterial tree of the lower extremities Involvement of large arteries common
4 Occurrence of superficial or migrating thrombophlebitis"	Occurs in 40% of cases	Does not occur This must be differentiated from secondary thrombophlebitis of superficial varicose veins which might be mistaken for "migrating phlebitis
5 Arterial calcification (by x rays)	None	Frequent
6 Complicating diseases a Hypertension	Incidence not greater than in general population	Frequent especially systolic hypertension
b Diabetes Mellitus	Incidence not greater than in general population	Frequent usually associated with a fulminant and severe course of the vascular disease
c Other evidence of arteriosclerosis	None	Frequent e g aortic sclerosis of retinal arteries presence of arcus or circulus senilis arteriosclerotic heart disease cerebral arteriosclerosis non obliterative sclerosis of other peripheral arteries e g the brachial and radial arteries

the condition is a widespread one involving most of the vessels of the body Characteristic lesions seen in the temporal arteries show a non suppurative granulomatous inflammation with a peculiar destruction of the elastic fibers of the internal elastic lamina with giant cell formation [157 158] With extension of the process there is destruction of the muscle fibers in the media intimal necrosis or intravascular thrombosis Involvement of the adventitia and even the periarterial nerves occurs in severe cases Healing takes place with granulation and fibrosis [127]

Arteriovenous fistulae [57 6 159 17] This is a condition *affecting the larger arteries and* veins where arterial blood is shunted directly

tips. Acrosclerosis follows sooner or later and in some cases a clinical picture develops that is not easily distinguishable from generalized scleroderma. The upper extremities are involved long before the lower.

While this entity has previously been considered a spastic disorder due to primary changes in the autonomic nervous system, the investigations of Lewis, Pickering and others indicate the likelihood of its being rather a primary vascular disorder affecting small arteries. Cases exhibiting secondary Raynaud's Phenomenon discussed under primary nervous disorders do not ever seem to progress to true Raynaud's disease. Thus it would appear reasonable to assume that the vascular changes (fibrotic thickening of small arteries) observed in Raynaud's disease are primary and not a sequela of prolonged or repeated spastic vascular contraction.

*Erythermalgia** [19, 195] is a vascular disorder characterized by abnormal vasodilation in the extremities causing redness and congestion of the involved parts with elevation of the surface temperature associated with burning and painful sensations. The condition is provoked and aggravated by dependency and exposure to heat. The patency of peripheral vessels is unimpaired with preservation or even increase of palpable peripheral pulsations. Clinically two types are recognized: an idiopathic type, the etiology of which is unknown and which occurs in otherwise healthy individuals who do not manifest any evidence of vascular or nervous disorders, and a secondary type where erythermalgia is associated with other diseases, e.g., polycythemia vera, generalized vascular disease, organic neurologic disease or heavy metal poisoning. In the primary or idiopathic type where there is absence of vascular insufficiency, complications such as ulcers or gangrene do not occur.

Acrocyanosis [18, 19, 199] is another vascular disorder whose etiology is unknown. It is characterized by vasospasm of the arterioles and dilatation of the capillary and venous plexuses of the hands and feet. Clinically the condition presents itself as an unevenly mottled blue or reddish blue discoloration of the involved parts which is intensified by exposure to cold. It is often associated with subjective and objective coldness; hyperhidrosis is common. Interpretation of the clinical significance of such vasomotor phenomena is difficult since they are often found in persons manifesting emotional instability.

*Livedo Reticularis** [185, 200] is a peculiar condition of unknown etiology characterized by a reddish blue mottling of the skin. It seems associated with proximal obstruction or spasm of small arterial branches and with distal capillary dilatation. The condition is persistent, not dependent upon environmental temperature changes and is occasionally associated with superficial ulcerations.

Cutis Marmorata [199, 200] is a term applied to a condition characterized by bluish marbleization of the skin on exposure to cold. Its appearance is very similar to livedo reticularis but is distinguished from the latter condition by the fact that it occurs and disappears transiently depending upon the environmental temperature. The condition is not demonstrably related to vascular disease.

Frostbite [138, 195, 193] Exposure to extremely low temperature obviously may cause death of tissues by freezing of the protoplasm. Exposure to somewhat higher temperatures (14 F), however, is followed by marked nutritional impairment of the tissues sufficient to cause their death and to lead to gangrene. Usually the use of the term frostbite is limited to gangrene following such exposure in cases where there was no pre-existing arterial disease. It stands to reason, however, that relative arterial insufficiency which otherwise may remain undetected renders a person much more liable to damage through exposure to cold. The acute phase of the condition is characterized by intravascular thrombosis involving arterioles, venules, small arteries and

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* Syn. erythromelalgia

* Syn. livedo racemosa, livedo annularis, asphyxia reticularis

ules erythematous eruptions bullous lesions purpura petechiae livedo reticularis necrosis *Disseminated lupus erythematosus* similarly is characterized by lesions occurring in many organs particularly involving the blood vessels Unlike polyarteritis which presents a picture of inflammation its lesions are mainly degenerative Furthermore it affects only the very small branches of the vascular tree namely the arterioles and capillaries The lesions characterized by widespread fibrinoid degeneration with minimal leukocytic infiltration, are also not confined to the vessels but are equally demonstrable in the surrounding tissues All the arteriolar coats may be involved with marked *intimal thickening True thrombosis however* is rare Clinically the principal lesions are cutaneous cardiac or renal The initial skin lesion in typical cases is an erythematous butterfly patch across the bridge of the nose although in many instances cutaneous lesions may appear elsewhere without the initial patch In the heart there might be an atypical verrucous endocarditis (Libman Sacks syndrome) causing cardiac decompensation which may be indistinguishable clinically *from subacute bacterial endocarditis In the* kidney lesions in the glomerular tufts appear as wire loop capillaries and focal necrosis causing signs and symptoms of glomerulonephritis Diagnosis is made by the finding of L E cells (neutrophils with engulfed large round homogeneous basic staining bodies) in the bone marrow or peripheral blood by the demonstration of the L E phenomenon or by biopsy This disease is much more frequent in females and its incidence is greatest in the second to the fourth decades of life [47, 176, 178] It is noteworthy that disease entities such as L E D in which the involvement of the vascular system is not as prominent a feature may present as peripheral vascular disorder with the signs of occlusive disease and even peripheral gangrene This is especially so in the presence of severe anemia

Dermatomyositis and Scleroderma do not present vascular lesions of any pathognomonic significance Increase in connective tissue with thickening of blood vessel walls, occasionally associated with thrombosis has been described Certain capillary changes have been described in the skin of these patients that are indistinguishable from the giant capillary loops observed in patients with Raynaud's disease [179] Many patients with dermatomyositis and especially with scleroderma also manifest symptoms of Raynaud's disease It is likely that such capillary changes are demonstrable only in those cases which are afflicted with both diseases

There is an increasing tendency to include rheumatic fever and rheumatoid arthritis among the fibrinoid diseases The vascular involvement in rheumatic fever has been described earlier in the chapter The vascular changes in rheumatoid arthritis are not characteristic However a fibrinoid change in the fiber bundles of the thickened synovial membrane may in a few instances be seen with the picture of the rheumatoid nodule This consists of a vascular granulation tissue the arteriolar walls may be found to be inflamed or necrotic and to contain fibrinoid material A vascular basis as the starting point *for the morphogenesis of the nodule has been* postulated due to the occurrence of the fibrinoid change and necrosis in relation to the vessel suggesting that a necrosis producing agent is fluid borne into the tissues from the vessels [180, 181] Advocates of this theory also believe that while *arteritis found in this disease is not histologically pathognomonic it is possibly a specific manifestation of the disease* They base this opinion on the description of arteritis in striated muscles (in 10% of biopsy specimens[18]) and the exclusive involvement of *the very small arteries and capillaries* Similar vascular lesions have been demonstrated in other tissue including the nerves[183] and heart [184]

Raynaud's Disease[18, 191] is characterized by frequent attacks of sudden blanching in several finger or in the whole hand elicited by exposure to cold (Raynaud's Phenomenon) and followed soon by the development of multiple small gangrenous ulcerations at the finger

and more lose its venous pitting character and become brawny There may be marked collateral enlargement of the superficial venous system or complicating ulcers may develop

Recurring thrombophlebitis has been decribed in the literature [03] It appears to be of an infectious nature but the exact mechanism is not known The superficial saphenae are most frequently involved

The smaller veins may be affected secondarily in syphilis Similarly secondary involvement of the veins may occur by extension of a tuberculous process from neighboring tissues

Migratory Phlebitis This condition is characterized by thrombophlebitis of short segments of many peripheral and visceral veins with minimal inflammatory reaction These are not involved simultaneously but rather in a skipping fashion The veins of the extremities the inferior vena cava and its tributaries and the dural sinuses are sites of predilection Small red tender nodules along the cour e of the vein may be seen with the peripheral lesions The etiology is unknown Some cases are associated with carcinoma of the pancreas [04] As mentioned previously a superficial migrating phlebitis may be the prodrome of thromboangiitis obliterans Focal infection has been invoked as the cause of this form of phlebitis [136] Obviously simple phlebitis occurring in varicose veins may partake of this characteristic Another variety of migrating phlebitis that has a special predilection for such visceral veins as the lungs heart and brain has been reported in the literature [0 07]

Varicose Veins As is the case in post phlebitic occlusion of deep veins collateral enlargement of the superficial veins may also occur in any condition where there is obstruction of the venous flow e g in pregnancy pelvic and abdominal neoplasms These must be differentiated from superficial varicosities mentioned above which represent collateral circulation in response to deep venous obstruction The ordinary run of the mill variety does not reflect the presence of deep venous disease it is probably the result of postural strain in association with congenitally incompetent or weak valves and/or a congenital weakne s of the venous wall (Ledderhose)

MINUTE VESSELS

Trench Foot * [08 10] Prolonged exposure to low but not freezing temperatures especially under damp or wet conditions can cause severe damage to the skin blood vessels or nerves of the expo ed upper or lower extremities Exposure to cold causes vasoconstriction and diminished blood flow to the extremities Persistent tissue anoxia in turn causes damage to the capillary walls and vascular occlusion In the chronic pha e of the disease [116] despite recanalization of thrombosed blood vessels or development of collaterals that obviate tissue death and necrosis a residual impairment of blood flow regulation and consequent difficulty in adjusting to temperature changes persist *A symptom comparable to intermittent claudication* in cold weather is also common and in some cases signs of occlusive vascular disease are evident

The presence or absence of pre existing arterial di ease at the time of exposure is a decisive factor in the clinical course of the resultant condition By and large where there is impaired arterial blood flow to start with there will be little tendency to recanalization and tissue death will ensue where the peripheral circulation and its regeneration were perfectly normal one finds the signs of rapid canalization in most instances In the chronic phase of the disease one may be guided in the clinical evaluation of the patient by the principle that the more discrepancy there is between the intensity and duration of exposure and the severity of the le ion the more likely it will be that the patient had diseased blood vessels already when he contracted the thermal injury the easier restitution occurs the more likely it is that the subject had a healthy vascular system before the exposure [01]

Telangiectasia [80 1 7 199 11 1] is a term

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* Syn immersion foot immersion hand sh lter foot

small veins While it presents the signs of occlusive arterial disease the early trophic changes are of a severity exceeding what one would expect from the degree of arterial involvement compared with chronic occlusive arterial disease [201] It is uncertain whether the intravascular thrombosis that occurs under these circumstances is due to the sustained vasoconstriction and vascular stasis or is secondary to the necrotic tissue changes

Pernio * [18, 199] This is a condition which appears to be another reaction of the peripheral blood vessels upon exposure to cold it is not known whether it represents a variety of *frostbite* However, most writers classify the two conditions separately and this might be the best thing to do until the e conditions are better understood Chilblains are said to occur in persons having feeble peripheral circulation' The acute form is encountered following exposure to cold it affects the exposed parts of the body (hand feet shin) and appears as an erythematous patch usually bilateral and symmetrical blanching on pressure cold to the touch and attended by tenderness itching and burning There is infiltration and edema of the affected part In more severe forms a purpura like rash may be seen and swelling and bleb formation are not uncommon Subsiding of the condition and eventual clearing of the lesion is the rule although a residual pigmentation in the area may remain

If the susceptible individual is repeatedly exposed to cold the chronic variety may be produced This form is characterized by seasonally recurring dermatitis in the same exposed parts of the body as those involved in the acute form The lesions are also seen as erythematous patches presenting various shades of red yet cold to the touch and with much of the same subjective manifestations More severe forms are hemorrhagic superficial ulcerations being not uncommon There is usually subsiding and clearing of the lesions during summer months with repeated recurrences during the cooler months, however permanent sequelae eventually appear in the form of residual scars from the ulcerations and atrophy of the skin and subcutaneous tissues at the sites of involvement

Erythema Ab Igne [199, 202] the virtual parallel to chilblains is due to the opposite cause namely heat The anterior surface of the legs is usually involved although other parts of the body which have been exposed to undue heat may similarly present the lesions It is seen in cooks stokers and other persons whose occupations expose them to direct heat from stoves furnaces and the like The lesions are erythematous with varying shades of red at first diffuse but ultimately presenting a reticulate pattern Pathologically va odilatation occurs and with continued exposure and progression of the condition secondary skin changes take place including pigment deposits in the involved areas Residual pigmentation may persist even after subsiding of the erythema

Aplasia or Hypoplasia of peripheral arteries are rather rare congenital conditions They are almost invariably bilateral General evaluation of the patient is necessary to differentiate the condition from acquired arterial disease The determination of the presence or absence of signs or symptoms of vascular insufficiency is of prime importance Where any doubt remains angiography establishes the diagnosis

VENOUS SEGMENT

Venous thrombosis (thrombophlebitis) may resolve completely (restitutio ad integrum) Even in cases with several recurrences of deep thrombophlebitis there may be intervals of complete recovery In about half the cases however there develops a state of permanent deep venous blockade characterized clinically by pitting edema heaviness of the limb and impaired functional capacity with pain on exertion This may conveniently be called *post phlebitic syndrome* It may occur after the first bout of thrombophlebitis or after a number of later bouts Over the years a lymph stasis supervenes and the swelling may more

* Syn. chilblains erythema pernio

which makes it compressible These cavernous spaces may directly connect with the larger channels in the systemic circulation in which case they usually behave like an arteriovenous fistula Malignant degeneration may occur rarely

Glomus Tumor * [1, 7, 18] Glomi are physiologic structures present in large numbers in the skin of the fingers and toes in smaller numbers in the hands and feet They are subcutaneous arteriovenous anastomoses with nonmyelinated nerve fibers and connective tissue enclosed by a smooth muscle coat These neuromyovascular structures serve as the body's thermostats and play an important role in peripheral circulation and heat regulation of the body A glomus or several of them may undergo benign hypertrophy and hyperplasia producing small rounded elevated firm red to blue extremely painful nodules 0 5 to 2 cm in diameter These may be found in various parts of the extremities but most frequently beneath the nails

Hemangiopericytomas [1, 6, 17, 19] are similar to the glomus tumor except that here the glomus arrangement is not preserved they are more varied in their location and are quite prone to become malignant

Lymphangioma [1, 7, 13] Benign tumors of the lymphatic channels are called lymphangiomas Like hemangiomas they are congenital being misplaced remnants of fetal tissue that have developed into lymphatic networks or spaces which are usually not continuous with the normal channels The term simple lymphangioma has been used to designate local dilatations of lymphatic vessels as well as anastomosing small and medium sized vessels separated by thin connective tissue trabeculae These lymphangiomata are small warty excrescences composed of lymphatic capillaries and diagnosed by their lymphatic contents

A cavernous lymphangioma presents itself as an ill defined compressible mass of varying size It may be located anywhere in the body It is not continuous with the normal channels but consists of a closed system of freely intercommunicating spaces lined by flat endothelium and separated by thick septa of connective tissue

A cystic lymphangioma * may present as a frankly fluctuant mass due to the fact that it consists of smaller and larger cystlike structures lined by endothelium and filled with lymph

Although generally benign tumors of lymphatic channels may in the course of extension or enlargement produce various clinical syndromes due to pressure on vital structures They may cause pressure on and obstruction of vascular channels to which they are usually in intimate anatomical relation

Malignant tumors [80, 1, 19, 30] arising from the blood vessels are called hemangiosarcomas those arising from the lymph vessels lymphangiosarcomas

The hemangiosarcoma † is malignant vascular tumor that is usually large ill defined often hemorrhagic and moderately firm in consistency It is composed of intercommunicating vascular channels lined by atypical endothelial cells These endothelial cells may also exist as sheets within the stroma or may be found in heaps in the vascular lumina

Kaposi's Sarcoma ‡ [47, 139, 1, 6] This is an especially interesting form of hemangiosarcoma that mostly occurs late in life While it may arise in almost any part of the body the initial lesion usually originates in the skin of the extremities These lesions appear as circumscribed discrete or grouped irregular red maculopapular lesions of pinhead to bean size gradually they acquire more hemosiderin pigment and become purplish and eventually black Purpuric lesions with vascular thrombosis also occur The process starts with lymphocytoid cells of Marchand and other vessel wall elements Soon the lesions exhibit

* Syn glomangioma angioneuroma painful subcutaneous nodule glomyoneuroma

* Syn cystic hygroma

† Syn hemangioendothelioma

‡ Syn multiple idiopathic hemorrhagic sarcoma idiopathic multiple pigment sarcoma Kaposi

used to designate abnormal dilatations of capillaries and other minute superficial blood vessels Such dilatations may be hereditary or acquired developing during life The following five common clinical types observed in the skin and mucous membranes have been studied by capillary microscopy and described in some detail

a *Simple telangiectasias* Seen as either red or blue in color not raised above the skin surface non pulsatile varying in length and diameter and involving a single portion of a vessel They are found especially on the nose and upper cheeks and occasionally on the upper chest

b Arborizing telangiectasias Except for the presence of some branch formations they are similar to the simple type in characteristics and distribution

c Spider telangiectasias They present as a rule a pulsating central raised bright red portion from which emanate fine radiating branches that measure one to two centimeters in diameter and a bright pink capillary flare between the radiating vessels By the exertion of slight pressure with a glass slide one can easily demonstrate pulsation which in many instances may even be palpable Pressure on the central spot with a fine point will cause immediate blanching of the whole lesion They occur chiefly on the upper limb the upper chest and back and at the sites of the simple *and arborizing telangiectasias They are frequently observed in patients with cirrhosis of* the liver or with nutritional deficiencies and in pregnant women They also occur however in healthy individual and may be found in association with other vascular lesions

d Papular telangiectasias They are round sharply circumscribed dark red papular stigmata varying in size from pinpoint to 1 0 cm diameter Microscopically they are seen as accumulation of tortuous capillary loops with multiple and curly crossing giving the loop an almost grapelike appearance They are most frequently seen on the trunk especially in elderly persons

e *Hereditary hemorrhagic telangiectasias* * This hereditary or congenital condition is characterized by the presence of groups of thin walled, abnormally dilated capillaries and small veins found in the skin but mostly in mucous membranes The lesions are small pinpoint to a few millimeters in diameter but are multiple and usually coalescent Bleeding *occurring spontaneously from* some lesions frequently gives rise to considerable blood loss and marked anemia

Vascular Tumors[141 13 1] Benign tumors of the vascular system are called hemangiomas Primary tumors of the vascular system may affect blood flow mechanically by pressure or obstruction or through the establishment of *abnormal shunt They may involve* the vessels in any organ or tissue of the body With possibly few exceptions vascular tumors are histologically similar to one another all being composed of vascular channels and classified only on the basis of the size and gross appearance of the lesions They result from the failure of the embryonic angioblasts to form the normal vascular channel

The capillary hemangioma is small ranging from a few millimeters to several centimeters in diameter It is bright red and made up of thin walled capillaries It is congenital but becomes clinically noticeable at later age When it undergoes retrogressive changes it is called sclerosing hemangioma

The portwine stain or nevus flammeus is pink to purplish flat and blotchy composed of thin walled dilated capillaries

Spider angiomas are really telangiectasias and not tumors they have been described in a previous section

The cavernous hemangioma is the biggest *type of benign vascular tumor* it usually occurs in the deeper portions of the skin and subcutaneous tissues for which reason it appears as an ill defined colorless or bluish mass It consists of a mass of intercommunicating cavernous spaces lined with endothelial cell

* Syn familial livoid telangiectasia Rendu Osler Weber disease

Table II

Influence of a Standard Vasodilator Stimulus (Gibbon Landis Procedure) on the Temperature and Blood Flow of the Lower Extremities Under Basal Conditions After Adaption to an Environment of 20 C and 55% Humidity

Patient's Initials	Basal Readings Temp C	Basal Readings Blood Flow (ml/100 ml tissue/min)	Maximum Response Temp C	Maximum Response Blood Flow (ml/100 ml tissue/min)	Nature of Response Temp C	Nature of Response Blood Flow (ml/100 ml tissue/min)
M N	24 0	6 7	32 0	8 5	Incr 8 0	Incr 1 8
M S	24 5	4 3	27 5	7 2	Incr 3 0	Incr 2 9
L J	23 0	8 4	32 5	12 3	Incr 9 5	Incr 3 9
M G	[illegible] 5	6 7	3[illegible] 5	10 0	Incr 10 0	Incr 3 3
E I	21.5	16 6	28 0	35.5	Incr 6 5	Incr 18 9
M E	[illegible]4 0	3 9	26 0	4 3	Incr 2 0	Incr 0 4
E H	24 0	10 7	[illegible]6 5	15 5	Incr 2.5	Incr 4 8
A R	26 5	6 4	34 0	10 0	Incr 7 5	Incr 3 6
C J	24 0	5 5	33 0	7 1	Incr 9 0	Incr 1 6
M M	22 5	10 2	34 0	15 3	Incr 11.5	Incr 5 1
S T	22 5	13 6	[illegible]4 0	25 7	Incr 1 5	Incr 12 1
C C	24 0	4 1	3[illegible] 5	4 5	Incr 8 5	Incr 0 4
Av Values		8 1		12 99		Incr 4 89

and in poliomyelitis are fully explained by disuse they are reversible and not associated with altered vasomotor responses [3, 191]

In Syringomyelia and in certain cases of tabes dorsalis an element of sensory disturbance is added to disuse leading sometimes to vascular changes secondary to trauma [3]

The effects of transection of the cord upon blood flow and vasomotor responses seem to be entirely dependent upon the level and completeness of the lesion [9] which two factors determine the degree of interruption of sympathetic pathways [34]

3 Peripheral Nerve Lesions Section or other injury of a peripheral nerve leads to reddening and warmth in the supplied limb As Lewis[191] so clearly analyzed it There are the expected sequels of simple sympathectomy After 2 to 3 weeks however there is a change to the opposite the limb becomes first cold and pale later slightly cyanotic If regeneration of the injured nerve is possible these findings may gradually disappear again If denervation persists there may ensue secondary vascular changes [189] If there is loss of sensation injuries may lead to severe sequelae reminding one of the indolent ulcers seen in syringomyelia

Causalgia is a term originally coined for cases with peripheral nerve injury without complete severance of the nerve which leads to an irritation rather than a degeneration of the posterior root system the sequelae a burning pain gave the name which should really be causalgia In recent years the term has been widely applied to all kinds of ill defined complaints most of them probably representing conversion symptoms

4 Disturbances of the Autonomic Nervous System The effects of sympathectomy upon peripheral blood flow and upon vasomotor responses are of great interest Obliterative arterial disease of the lower extremities does not essentially alter the reflex vasomotor responses to warming although basal rest flow is considerably lower than in young healthy adults while subjects of comparable age groups without demonstrable vascular disease show intermediate values

It is of interest that response of surface temperature to warming is delayed and takes place in a more gradual fashion in arteriosclerotic subjects (See fig 2)

After sympathectomy rest flow and surface temperature are increased [37, 41] Most workers agree that sympathectomy alters vasomotor responses [36, 4, 49] There is suggestive evidence that the neural mechanism dominates

changes characteristic of capillary or cavernous hemangioma. Infiltration of the surrounding tissues may produce an elephantiasic appearance. As the condition progresses the lymphocytoid cells become replaced with elongated spindle-like cells that fuse with and resemble endothelial cells, producing a sarcomatous appearance. Sooner or later new lesions appear in other parts of the extremities as well as in mucous membranes, lymph nodes and most any of the viscera, notably the liver, intestines, lungs and spleen. It is not established whether these represent metastatic lesions or multiple primary foci. Hemorrhages and subsequent anemia are common; also instances of hemolytic anemia, some of which are presumably due to lesions in the spleen or in the bone marrow, have been reported. The course is fulminating in some and protracted for years in others.

Chapter 3 Alterations in Blood Flow Due to Extrinsic Causes

TRAUMATIC INJURIES

Traumatic injuries, with or without loss of continuity of the skin or tissue substance, if sufficiently extensive or severe, inescapably involve the various vascular channels in the affected extremity. This may result directly from the accident or from any supervening infection. Arteritis, phlebitis and arterial as well as venous thrombosis may develop. Secondary arterial and venous spasm frequently develop under these circumstances and occur in the blood vessels directly involved by the injury as well as other vessels in the immediate vicinity. This may be due to a reflex increase in vasomotor tone in the body's effort to control hemorrhage, or to the accumulation of metabolites resulting from the circulatory impairment. Segmental arterial spasm has been observed at the operating table even under minimal traumatic conditions.[2,7]

DISEASE AND INJURY OF THE NERVOUS SYSTEM

1 Cerebral lesions (cerebrovascular accidents, tumors). These do not seem to influence peripheral blood flow and vasomotor responses to any great extent unless one of the vasomotor centers is involved. As a matter of fact, marked vasomotor alterations occurring in a case with a cerebral lesion strongly suggest a hypothalamic involvement.[2,8] The slight increase in basal flow regularly observed in the paralyzed extremities of hemiplegic patients does not seem to bear any relation to disuse.[2,9] Vasomotor responses to physiologic and pharmacologic stimuli are preserved.

Much attention has been paid to alterations in cerebral blood flow, since a great number of cerebral lesions may be traced etiologically to vascular disease.[30,31] Arteriosclerosis and hypertension have a widespread and widely known impact upon cerebral circulation[3] and brain metabolism[31] and thus necessarily upon brain functions. It is accepted knowledge that most "strokes" are etiologically due to vascular disease.[30] The occurrence of cerebral arterial spasm has been more controversial than that concerning "peripheral arterial spasm." It seems that the evidence is in favor of the existence of such a clinical entity,[3,24] although perhaps not as clear cut as those concerning arterial channels in the extremities. It would be outside the scope of this book to discuss these extremely interesting problems. The involvement of cerebral circulation by a rarer type of vascular disease, such as obliterative thromboangiitis, and the implications of the occurrence of congenital and later developed aneurysm of cerebral vessels may also be mentioned in passing.

2 *Lesions of the Spinal Cord* Blood flow changes observed in muscular dystrophy

FIG. 2. SKIN TEMPERATURE RESPONSE TO G L PROCEDURE.

FIG 3 RESPONSE TO G L PROCEDURE.

Table III

Influence of a Standard Vasodilator Stimulus (G L Procedure) on Temperature and Blood Flow of Lower Extremity Under Basal Conditions After Adaptation to Environment of 20° C and 55% Humidity

A NORMAL SUBJECTS (YOUNG ADULTS)

	TEMPERATURE C		BLOOD FLOW (ML/100 ML TISSUE/MIN)	
Patient	*Control Reading*	*Maximum Response*	*Basal Flow*	*Maximum Response*
I W	28.5	35.0	13.6	17.7
S D	24.0	35.5	9.1	18.0
S I	22.0	40.0	3.2	7.0
M H	24.0	34.5	24.0	25.4
D S	22.5	36.5	20.9	30.5
E C	27.0	34.5	10.5	14.8
A O	27.5	33.5	16.0	21.6
S P	23.0	33.5	16.7	18.9
A S	26.0	33.0	14.5	24.4
E G	24.5	33.5	9.4	20.8
		Average Value	13.79	19.91

B ELDERLY SUBJECTS (NO DEMONSTRABLE VASCULAR DISEASE)

F K	25.0	34.5	3.6	5.9
W F	25.0	35.0	3.4	6.5
H T	23.0	32.5	10.5	12.1
J J	25.5	31.5	8.4	14.2
J B	22.5	25.0	8.6	10.1
J H	23.0	29.5	15.9	22.[illegible]
M.S	23.0	33.0	10.5	14.8
J F	21.5		5.7	9.9
E V	22.5	34.5	8.3	12.2
		Average Value	8.32	12.03

C ELDERLY SUBJECTS (WITH OBLITERATIVE ARTERIAL DISEASE)

R K	25.0	26.0	2.8	6.9
J O	21.5	29.0	2.0	3.9
J K	24.0	30.5	2.3	3.2
M F	24.0	31.5	3.2	9.7
M G	25.5	32.5	4.4	6.2
M N	25.5	34.0	2.3	4.9
O B		35.5	2.8	5.1
A D	24.0		6.0	9.4
		Average Value	3.23	6.16

in bringing about predispo ing periarthritis [f] In its fullblown appearance the symptom complex which has also been described as houlder hand syndrome [16] exhibits all manife tations of neurovascular sympathetic irritation pain discoloration limitation of motion muscular atrophy and spotty osteoporosis (Sudeck s bone atrophy)

For many years the term va oneuro es (angioneuroses) has been used to denote anything from demon trable arterio pastic disorders to uch vague concepts as 'capillary neuroses [17] [f8] Functional di turbances in blood flow as far as they are measurable or at least clinically demon trable and traceable to faulty innervation have been di cussed under specific headings Our factual knowledge of such disturbances in the minute circulation is extremely limited and mo t writings on the ubject have been highly speculative Use of the term vasoneurosis or angioneurosis doe not appear justified

DISTURBANCES IN THE ENDOCRINE SYSTEM

The secretions of endocrine gland are carried by the blood throughout the body and may affect any organ or system The vascular sy tem seems to be under the influence of everal of these hormones (Part I) Recognition of the close relationship between endocrine hormones and the autonomous nervous system [f9] [0] on the one hand and the importance of sympathetic pathways for vasomotion on the other hand could hardly fail to draw the attention of workers in both the endocrine and the vascular fields of research Nevertheless our knowledge of specific pathologic conditions concerning one or more endocrine gland is very limited

1 The Thyroid It is a well known ob ervation [0] [71] that the skin of hypothyroid ubjects tends to be cool and dry and that these individuals are inclined to feel cold very ea ily under environmental conditions generally considered comfortable the exact opposite applies to patients with a hyperactive thyroid In the older literature the terms hypocirculation and hypercirculation have been used respectively in myxedema and in Graves Disease [7] It seems logical to assume that the va cular responses involved are reactive to the changes in metaboli m [3] rather than to a specific vascular action of the thyroid hormone It is of interest that an inhibition of kin capillary development has been shown to be regularly demonstrable in congenital myxedema [8] [4] Development of skin capillaries to normal adult forms in treated hypothyroid children has likewise been observed [8] [5]

2 The Adrenal Medulla and the Chromaffine System Catechol amines (adrenaline noradrenaline and possibly others) are in all probability the substances which mediate va oconstriction at the place of neurohumoral transmis ion in the ves el wall Their role in the specific form of hypertension due to phaeochromocytoma is unquestioned [76] [77] What etiologic significance if any they have in es ential hypertension is unknown [8]

3 The Adrenal Cortex Peripheral blood flow to the extremities has never been shown to be directly involved in adrenocortical hyper or hypofunction To even touch upon the intricate relationship of adrenocortical secretion to essential hyperten ion and to shock is not within the scope of this book

4 The Gonads The search for influence of gonadal secretions upon peripheral blood flow has hardly advanced since the early observation that ovarian extract inhibits the visual disappearance of kin capillaries following the administration of adrenaline [8] Sporadic report appeared in the literature on the u e of gonadic steroids in occlusive disease of peripheral arteries Such trials were based on the results of animal experiments [80] [81] Like other investgiators we have not been able to demonstrate that mea urable changes in peripheral blood flow in man are attributable to action of gonadic steroids Connection of some disturbances in peripheral circulation to the gonads has been su pected on the basis of sex distribution i e the comparative rarity of obliterative arterioscléro is in non diabetic females higher incidence of obliterative thromboangiitis in

the regulation of flow through the vascular bed of the skin (See fig 3)

Surface temperature does not fall with the decrease in blood flow in the sympathectomized limb in response to body warming the resulting lack of correlation between changes in surface temperature (which reflects blood flow in the vascular bed of the skin) and total blood flow to the limb (which may be taken to be predominantly representative of blood flow to the vascular bed in the muscles) suggests that there are different and separate mechanisms regulating vasomotor responses in these beds Confirmatory evidence has been presented recently by Edholm and his co workers [0, 1] Furthermore the fixation of surface temperature (skin blood flow) indicates that blood flow to the skin is primarily under neural control while blood flow to the muscles is influenced to a much greater degree by other regulatory mechanisms

Recent observations [37] suggest the possibility of influencing reflex vasomotor responses in sympathectomized limbs toward normalization by adrenergic blockade This possibly implies that circulating catechol amines play a considerable role in these responses Much further investigative work is required to establish a possible linkage to the classical findings of Cannon and his co workers [3, 7] concerning the sensitization of denervated structures to adrenaline

At the time of this writing much remains unknown about the role of the autonomic nervous system in influencing peripheral blood flow The fact that purely psychic (emotional) stimuli may have a visible and even measurable effect on vasomotion increases the difficulty in arriving at conclusions

The differentiation between vasoconstrictor and vasodilator disorders may be maintained at present as a workable classification for want of a better founded one it is well however to keep in mind that this classification is based upon a working hypothesis that is not entirely supported by facts

Various sequelae of a tendency to local peripheral vasoconstriction have been described A background of emotional disturbance seems to be invariably present in people who in the absence of organic vascular disease have attacks of sudden blanching of several fingers of the whole hand either elicited by exposure to cold or by emotional upset or both This phenomenon has been described as doigts morts or as peripheral syncope [9] The disease picture described by Raynaud as symmetrical gangrene [187] included this phenomenon as one of its features it is frequently called Raynaud's Phenomenon' Apparently it may occur superimposed upon occlusive vascular disease but a direct connection with the vascular disease has never been demonstrated The majority of patients with occlusive peripheral arterial disease do not exhibit Raynaud's Phenomenon The suspicion appears justified that the occurrence of Raynaud's Phenomenon in patients who have occlusive vascular disease is just incidental since it is not too rare in the population at large

Bone atrophy due to vasospasm was described by Sudeck [9] Sudeck's Atrophy [1] characterized by spotty osteoporosis which is also observed in reflex dystrophy (shoulder hand syndrome)

Vasospastic disturbances have been described as occupational disease in pneumatic tool workers [60] and pianists and typists the last two involving milder forms The fingers or hands show discoloration and the patients report a feeling of pins and needles or numbness Much more rarely we have observed the phenomenon in feet and toes of some people after prolonged standing in fast driving buses or trucks (transportation of soldiers) Occlusive disease following repeated occupational trauma has been observed [61]

Reflex dystrophy of an extremity more frequently the upper than the lower was originally described after injury or operation [] It has since been seen not infrequently after myocardial infarction [63, 64] and occasionally in cases of rheumatic heart disease It is of interest that in cardiac patients who exhibit this symptomatology the right upper extremity is involved almost as frequently as the left The etiologic role of disuse has not been clearly determined but it is presumed that it is a factor

bated question appears of relatively little significance since both are so closely connected[9, 79] The syndrome may be due to two types of anatomical anomaly muscular or skeletal[96] The muscle most frequently shown to have an anomalous course exerting pressure on nerve and blood vessels is the scalenus anticus less frequently the scalenus medius The skeletal anomaly responsible for the syndrome is a cervical rib Also costoclavicular compression has been found to be responsible for the syndrome in some cases[298] This type of neurovascular compression can be elicited by having the patient force the shoulder backward and downward The syndrome occurs most frequently *unilaterally only rarely bilaterally* Differentiation from brachial neuritis is sometimes not easy however deep inspiration turning the head to the affected side or elevating the arm may produce palpable diminution or even disappearance of the homolateral brachial and radial pulse[299] It has been shown by Wright[300] that abnormal position of arms during sleep may produce the syndrome Complicating thrombosis of the subclavian vessels is a rare but, of course very serious occurrence[301]

Arthritic and other orthopedic deformities may cause local disturbances in blood flow These rarely concern arterial supply frequently however they apply to venous drainage and sometimes minute circulation through localized pressure even to the degree of superficial (decubital) ulceration

Secondary hypervascularization accompanying excessive apposition of bone may act like a large arteriovenous shunt with all its sequelae This occurs in progressed cases of Osteitis deformans (Paget s Disease)[177]

CHANGES IN THE COMPOSITION OF THE BLOOD

Various blood dyscrasias are known to affect the permeability of the capillaries and to cause punctate or even larger extravasations Thrombocytopenia and various forms of leukemia may be mentioned here The mechanisms at play are unknown Reduced coagulability of the blood per se is hardly a sufficient explanation since patients may have a prolonged prothrombin time without any extravasation Increased capillary fragility seems largely unrelated to the state of blood coagulability

Patients with polycythemia vera (primary polycythemia) are reported to have an increased tendency to thrombosis[185] This does not apply to patients with secondary polycythemia due to chronic pulmonary disease

In 1937 Nygaard and Brown described an entity they called *essential thrombophilia* This rare condition leads to multiple venous and arterial thromboses[30] Increase in number and *changes in physical properties of platelets as* well as increase in globulin and fibrinogen content of the serum have been demonstrated[303] in these cases On the other hand there is a rare form of thrombocytopenic purpura[304] described as thrombotic thrombocytopenic purpura where a reduced number of platelets is associated with multiple thrombus formation in small vessels It is actually difficult to decide whether both of the above discussed conditions should be classified as primarily vascular or hematologic

SENSITIVITY REACTIONS

Since the classical description by Lewis of the triple response in the minute blood vessels of the human skin to mechanical stimulation (dermographia) and to histamine it has been recognized that the wheal (as produced by histamine instillation) is the basic lesion of most hypersensitivity reactions It has been known that the minute vessels in the mucous membranes may exhibit the same type of response Nothing is known about the capillary reaction in parenchymatous organs

The reaction may be seen unaltered or widely modified in *vascular sensitivity reactions to cold* There are patients who develop a giant severely itchy urtica upon immersion of their hand or feet in cold water involving exactly the immersed portion these same patients report general sensitivity to cold producing burning pain itching and swelling of the ex

males and higher incidence of Raynaud s dis ease in females Conclusive evidence however is lacking It may well be that the recently started investigation of the role gonadic ster oids play in the development of atherosclero sis [81 8] might furnish clues in re pect to sex linkage of peripheral va cular di ease

5 The Pancreas The observation of a peculiar bright pink color of acra (cheeks no e fingers toes) in diabetic patients was common in the pre insulin era [70 83] These pa tients regularly showed an abnormal dilatation of the capillary segment connecting the arterial and venou limbs when the involved areas were viewed under the microscope [58 84] It is in tere ting to note that this can no longer be ob erved in the in ulin treated case The mechan i m of the phenomenon is unknown

6 The Pituitary Pitressin a pressor sub stance ascribed to posterior lobe secretion is probably either secreted by intermediary lobe substance which has grown into the posterior lobe [0 8] *or produced by neurosecretory cells* in the hypothalamus and stored in the posterior pituitary lobe [80] It has a markedly constrict ing effect upon minute blood vessels in everal va cular bed [8 88] including the kin in man [70] At pre ent there are no data available which would clearly indicate a direct effect upon peripheral blood flow in any of the ac cepted clinical entities a cribed to pathologic changes in the pituitary

CHANGES IN GENERAL CIRCULATION

The relationship of va omotor responses in the extremities to the heart has been di cussed in Part I

Markedly dimini hed left ventricular output (e g in tight mitral tenosis) leads to mark edly dimini hed filling of the vascular system in the extremities with reactive constriction This may lead to all the equelae of diminished blood supply—including gangrene at the acra —and the condition may be difficult to differ entiate from primary va cular di ea e Evalu ation of the case as a whole and a good history will facilitate the decision A ball valve throm bus may cause a similar picture except that the phenomenon of diminished blood upply will fluctuate and affect various extremities at various times Many years ago Sahli described what he called hypercirculation in ca es of anemia and hyperthyroidism basing his as sumption of increa ed rate and velocity in pe ripheral flow on studies with the Gaertner tono meter [7] His assumption has been subsequently confirmed by more reliable method of mea ur ing peripheral blood flow [89] It is of consider able interest in this connection that in both anemia and hyperthyroidism failure has been hown to occur in the presence of increa ed cardiac output [49]

That tonus of the large thoracic veins may play a role in some of the mechani ms involved in cardiac failure has been widely di cu ed [90] The role extremity veins may play in homeo stasis of venous tone and pressure is unknown but is currently under inve tigation by Wil kins and his group [91]

The role of minute ves els in experimental shock has been studied thoroughly It has been hown on the capillary circulation in the mes entery and omentum of the dog and in the rat s mesoappendix that in the first (reversible) stage of hemorrhagic shock the blood ve sel exhibit constriction and hyper en itivity to adrenalin [9] It has further been shown that during this tage a vasoexcitor material (VEM) probably identical with renin is lib erated In the later (irreversible) state of hock the blood vessels dilate and their re sponsiveness decrea es In this stage a vasode pres or material (VDM) was found in the blood This i supposedly active through its ferritin content [93]

ABNORMALITIES OF THE MUSCULO SKELETAL SYSTEM

Scalenus anticus syndrome is a term ap plied to a symptom complex [94] cau ed by pres sure on the brachial nerve plexus and the sub clavian ves el Such pressure leads to pain discoloration and changes in perspiration and urface temperature It is not clear whether the symptomatology is primarily due to nerve irritation or to vascular pasm the much de

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po ed parts Gangrene of fingers and toes has been described as occurring with hemoglobin uria in syphilitic patients upon exposure to cold In some nonsyphilitic subjects exposure to cold has been found to produce hemag glutination accompanied by peripheral gan grene[191] Cryoglobulins have been found in the blood of such patients but al o in patients with Raynaud s disease[30]

It is hardly within the scope of this book to describe the sensitivity reactions to various drugs although some of them might well be primarily vascular Experimental work has been plentiful to show that sensitivity reactions in animals may produce vascular changes closely resembling some of those found in hu man pathology[300 30]

It is known that ' sensitivity angiitis may so closely resemble primary polyarteritis no do a[17] that workers in the field have found it necessary to painstakingly e tablish the differ ential diagnosis Recently di ease pictures have been described following the prolonged use of the hypotensive agent Hydrazinophthal azine that are indi tingui hable from rheuma toid arthritis in some instances from dis em inated lupus erythemato us in others[304]

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Part III Physiologic Responses to Disturbances in Blood Flow

Chap 1 Development of Secondary (Collateral) Circulation

Chap 2 Restoration of Primary Circulation

Spontaneous vasomotor responses to local disturbances in blood flow may be observed to be favorable or unfavorable in the sense of repair and restoration It may be stated that in general vasoconstrictor responses are unfavorable vasodilator responses favorable It is of considerable interest that the same stimulus may produce either vasoconstriction or vasodilation of the minute blood vessels respective to the smaller or greater intensity with which it is applied A light stroke upon the human skin with a blunt or pointed instrument produces a white reaction due to vasoconstriction via an axon reflex If the same type of stimulus is applied repeatedly or with greater intensity the triple response i e vasodilation is elicited This can be seen as a red reaction in the line of stroke accompanied by vasoconstriction on both sides of the line and the development of a capillary flare followed by wheal formation (passage of serum from the dilated vessels into the tissues) along the line of red reaction [1]

Vasoconstrictor responses in the larger extremity vessels have been observed following trauma and operations [3] as well as in response to thrombotic[4,5] and embolic occlusions [6]

It is conceivable that a vascular bed deprived of part of its blood supply might be aided by a vasoconstrictor response in another vascular bed causing shunting of blood to the place of need There is no conclusive evidence available at present to support this otherwise reasonable assumption

On the other hand vasodilator responses at the place of need have been observed both experimentally and clinically and the development of so called collateral circulation has been proven morphologically

Quiring has pointed out that there seems to be a certain degree of freedom in the final distribution of blood vessels as expressed in the many anomalies and variations of vascular patterns in the body It is conceivable that the physico chemical forces at play lead to the formation or further development of vascular channels where needed [8-13]

Chapter 1 Development of Secondary (Collateral) Circulation

The principal arterial channels to the extremities have been reviewed in Part I These vessels are primarily responsible for the blood supply of the limbs and are therefore referred to as primary principal or main stem arteries Along their entire course however branches are given off which not only supply the tissues in the immediate and farther neighborhood of the parent trunk but which in turn give off smaller twigs that meet or anastomose with similar twigs from branches arising at some other point from the same or another parent

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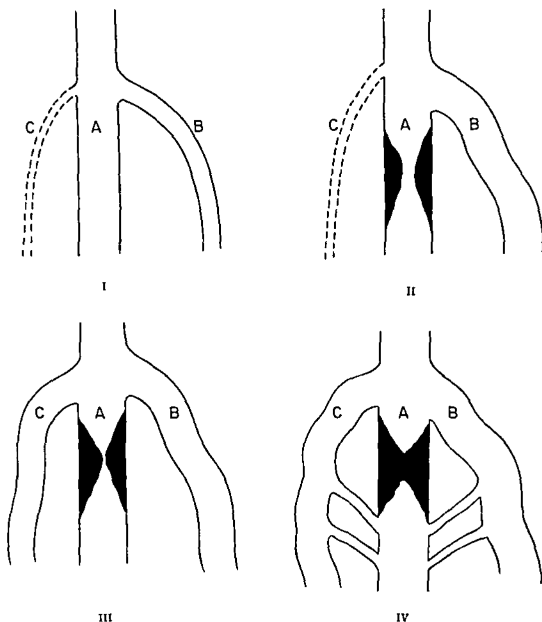


FIG 4 SCHEMATIC DRAWINGS DEPICTING THE DEVELOPMENT OF COLLATERAL CIRCULATION IN ARTERIAL OCCLUSION

I *Normal vessel* (A) Note the functioning side channel (B) and the nonfunctioning preformed channel (C)

II *Incomplete occlusion* The functioning side channel proximally to the occlusion has widened and become tortuous by elongation

III *Progressed occlusion* The nonfunctioning preformed channel proximally to the occlusion has become a functioning collateral

IV *Complete occlusion* Both collaterals have developed connecting branches to the main vessel distally to the occlusion

trunk Such anastomoses then form archlike vascular channels conveying blood in the same general direction as the main artery, compared to which they are much smaller in caliber These channels then are collateral secondary or accessory to the parent vessels from which they are anatomically and physiologically distinguished The primary vessels are larger in size and direct in their course and *they convey the greater portion of the vascular* supply to the part while the secondary or collateral vessels are smaller more circuitous and carry only a comparatively small portion of the blood Histologically these two groups of vessels are exactly alike

It is understandable that obstruction at any point in the principal arterial trunk is followed by a compensatory response in the channels bridging the occluded portion directed at taking over such function as can no longer be performed by the obstructed vessel Whenever the primary vessel is impaired in its entirety or almost so (as it happens in some forms of *generalized arterial disease) the collateral* channels alone assume the responsibility of supplying the part In that event the collateral vessel ceases to be an accessory and indeed becomes the primary channel while the original principal vessel may even be converted into a functionless cord

The adequacy of the circulation following obstruction of the principal vessel thus depends upon the ability of the collateral vessels to enlarge sufficiently to carry over the blood which would normally have coursed through the occluded channel Quiring[7] quoting Spalteholz expressed this mathematically If the sum of the squares of the cross sections of the anastomosing vessels equals or is larger than that of the square of the occluded artery the anastomosis is adequate

The pre existing anastomosing vessels which normally serve as accessory or collateral channels *are enumerated* and well illustrated in standard texts of anatomy Quiring gives an excellent and detailed discussion on collateral vessels the *reader interested* in the subject is referred to his book

Although the anatomic development of collateral circulation has been studied thoroughly in various organs the mechanisms at play are still not fully understood Physical forces like differences in intravascular pressure in the occluded vessel as *compared to that in the* collateral channels have been considered of prime importance The accumulation of carbon *dioxide*[14] *in the area supplied by the* occluded vessel has also been used as an explanation and nervous mechanisms set into motion by the occurrence of the occlusion have been demonstrated to play a role[15] Experimentally sympathetic denervation appears to influence favorably the opening of collateral channels induced by an artificially produced arteriovenous fistula[16, 17] Mulvihill and Harvey[10] reviewed some of the hypotheses that have been postulated to explain the production of collateral circulation and they confirmed on the basis of their experiments the operation of a vasomotor component According to Spalteholz[18] *the following factors are the main* determinants the extent arrangement and condition of the vessels in a given vascular bed the status of the general circulation the general condition of the body the time sequence of the occlusion and the animal species Briefly an adequate collateral circulation is likely to develop if the occlusion occurs in an area with a rich blood supply if the anastomotic vessels in the area arise from several vessels and if the walls of the collateral vessels are not diseased or otherwise incapable of dilatation Deficiencies in cardiac function hypotensive states diminution of blood volume below critical levels and disturbances in composition or viscosity of the blood adversely affect the development of collateral blood flow A good general condition of health in the individual and intactness of the venous system are essential in sudden occlusions the number and extent of the pre existing anastomotic channels are of primary importance while in gradual occlusions the condition and nature of the walls of these vessels are decisive Vascular

ure).[7-8] Such situations may frequently be observed in the lower extremities of people afflicted with obliterative arteriosclerosis. One is tempted to talk about diminished arterial reserve or local circulatory reserve, making these terms correspond to those used in discussing cardiac work performance.

In the event of sudden complete occlusion the blood available from pre-existing collateral vessels may be grossly inadequate to meet the needs of the part; the circumstances are, of course, rather unfavorable for the further development of the vessels. Moreover, there is hardly any time for the formation of new vascular channels. It is indeed amazing that, despite this condition, a part not infrequently recovers from what seemed to be complete embolic arterial occlusion. This happens more often in the upper than in the lower limbs. Whether this is due to the difference in vasomotor tone or to the presence of a more extensive and more efficient collateral network is still a matter of speculation.

In summary, anatomically the existence of three types of secondarily developed channels might be postulated: 1. Channels bypassing the primary route, pre-existing and in active use even prior to the occlusion of the primary channel, now being widened and lengthened (by meandering) and thus made more capable of carrying the additional load; these are collateral channels in the strict sense of the word. 2. Preformed (potential) channels, part of the arteriolar and capillary bed, which are not used permanently but are called upon when the necessity arises. 3. Newly formed channels.

The recently reported findings with the electron microscope[29] revealing interesting structural details of the capillary wall may well point the way to a better understanding of vessel formation under normal and pathologic conditions.

Chapter 2 Restoration of Primary Circulation

It would appear logical to talk about spontaneous efforts of the organism to restore function to the primary impaired blood vessels proper before discussing the various vascular responses leading to the development of collateral circulation. The fact is, however, that the body's means of restoring primary circulation in an occluded vessel are few and slow in action and in the overwhelming majority of instances are widely overshadowed by the manifestations of collateral circulation. There are only two known ways in which spontaneous restoration of passage through an occluded vascular channel can occur. 1. By canalization of an organized thrombus, which occurs only in larger vessels and usually after a lapse of many months or years. There are three forces at work in this process: vasa vasorum from the surrounding wall penetrate the plug, new capillaries grow in from the free end of the thrombus which has been covered with endothelium, and blind channels (rifts) within the plug become endothelialized and develop into new blood channels.[30] 2. Through relaxation of the vessel wall around a recent embolus, whereby occlusion recurs more distally as the embolus reaches narrower segments of the vessel. If the embolus finally lodges in an area with ample anastomosing circulation, its effects may be insignificant, as pointed out before.[31] Recanalization may logically be expected to occur more readily in large arteries than in small caliber vessels, since it is probably dependent upon the vis a tergo of the onrushing blood and the number of vasa vasorum present.[3, 36]

responses differ quantitatively and/or qualitatively among various species

With these considerations in mind it may be mentioned parenthetically that while the conditions for the development of collateral circulation in the heart muscle[10] may be different from those in the extremities there are striking analogies in the course of events following arterial occlusion

The discussion has been limited so far to the opening or enlarging of pre existing collateral channels An even less understood phenomenon is the apparent development of entirely new vascular channels in response to occlusion of primary vascular routes [3, 4] No explanation is offered However certain embryologic phenomena may make such new formations not entirely surprising or unexpected

First it may be recalled that the first vascular channels in ontogenetic development arise from mesenchymal cells and are capillary in nature[1] and from this diffuse capillary bed by confluence and fusion of smaller vessels and with further differentiations the larger vascular channels are formed The ultimate size of the vessel produced is proportionate to the amount of blood the vessel would be called upon to convey in the fully developed organism As the organism develops and grows two or more blood supply routes appear to form in an area Some of these remain undeveloped or are diverted to other areas or organs

Second the normal obliteration of fully developed vascular channels during embryonic and postnatal life is equally difficult to explain Some of these vessels are closed completely and transformed into solid connective tissue cords presumably because they have outlived their usefulness The Ductus arteriosus Botalli is an example of this phenomenon In other instances a fully developed vessel which originally forms the main vascular supply to a part somehow undergoes regressive changes or is arrested in its further development to give way to subsequently formed channels which then become the principal blood supply route to the same part The original channel may then persist only as a small contributory branch to the newly formed vascular set up An example of this condition is the ischiadic artery which is originally the main supply of the lower limb subsequently this role is taken over by the femoral artery and its branches the ischiadic artery only supplies contributory elements to the deep femoral and anterior tibial branches

Third the reversion and reassumption of embryonic functions by organs and tissues which have long lost those capabilities under conditions of need and stress is a well known clinical phenomenon The resumption of erythropoiesis by the liver and the spleen in cases of marked and severe anemia are illustrations of this phenomenon The mechanisms involved are unknown and one can only speculate John Hunter s empirical statement that blood goes where it is needed may indeed be altered to blood is sent where it is needed Thus the occurrence of obstruction in a vascular channel creates an emergency locally with an urgent need for blood in the area It is conceivable that under these circumstances the mesenchymal cells in the area revert to embryonic angioblastic activity forming new capillaries which in turn by fusion confluence and further differentiation, may form larger vascular channels

Physiologic responses to curtailment of circulation to a part seem to be directed mostly toward the development of what has been termed collateral circulation In chronic disease with slowly progressing vascular occlusion restorative efforts of the organism along these lines may be so successful as to present us with parts in which no evidence of open primary channels can be detected but which seem to have a perfectly sufficient blood supply by means of secondary developed channels it should be noted however that while circulation to such parts may be sufficient at rest or even with slight exercise it is usually not capable of coping with suddenly increased demands such as are called for by heavy exercise external injury or when circulation in general is interfered with (e g in heart fail

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Part IV Management and Therapy

THERAPEUTIC ATTEMPTS to correct disturbances in peripheral blood flow can be directed either at restoring the occluded primary channel or at enhancing the development of collateral circulation The approach may be by either *medical*[1] *or surgical means*[2] The disturbances in peripheral blood flow represent in most instances either manifestations of generalized vascular disease or complica*tions of an underlying extravascular disorder* In turn the disturbances in peripheral circu*lation may lead to complicating sequelae*

Chapter 1 Restoration of Occluded Primary Arterial Channels

MEDICAL MEANS

Complete occlusion of an arterial channel may be entirely organic (e g completely occluding thrombus) partially organic (e g partially occluding thrombus and superimposed secondary constriction of the vessel) or entirely due to reversible local constriction (so called spasm)

Arterial constriction (spasm) may be relieved by procedures and drugs capable of re*ducing vasomotor tone* Some of these procedures are said to be also capable of producing active vasodilation The simplest and most useful physiologic procedure *to relieve arterial* spasm therapeutically is the one devised by Gibbon Landis *Heat application to the chest* back and abdomen maintained for 50 to 60 minutes reflexly lowers vasomotor tone in the extremitie counteracts any vasoconstrictor stimulus at play and induces vasodilation

Pharmacologic release of vasomotor tone and thus of arterial constriction is best accomplished through the slow intravenous injection of either diethyl aminoethanol or such gang

lionic blocking agents as tetraethylammonium pentolinium or hexamethonium. While the alcohol does not cause any significant changes in arterial pressure the quaternary amines may produce marked hypotension especially of the postural type which may be elicited for several hours after administration of the drug by letting the patient assume the erect position. When tetraethylammonium chloride is used dramatic drop in resting pressure is less often encountered but postural hypotension is just as marked as with the more potent penta and hexamethonium. There are no direct medical means proven to help restore flow through an arterial vessel that has been occluded organically. The question whether anticoagulants may be helpful in slowing down organization of an occluding arterial thrombus and thus aid in its recanalization has still not passed the state of a fairly reasonable assumption.

SURGICAL MEANS

Localized obstruction due to thrombus formation or embolism may be managed successfully by surgical methods.

Thrombendarterectomy[3] the excision of thrombus with repair of the artery when successful restores an obstructed primary vascular channel and allows blood to recirculate through the same routes.

Arterial grafting attempts to re-establish a vascular channel which has been rendered unserviceable by obstruction. The various materials used for grafting have included pieces of a vein[4] artery or a cloth tube made of vinyon N Nylon Orlon or Dacron[5]. Vascular grafting may accomplish this aim in two ways either the obstructed part is resected and replaced by the graft or it is left *in situ* and bypassed by the graft.

Various reports of such reconstructive operations have been quoted as successful in 50-90% of cases and have listed maintenance of patency for 6 months or longer in 25-80% of these cases. In large measure success depends upon the condition of the rest of the vascular tree at the time of operation i.e. the likelihood of the graft's taking without rethrombosing varies inversely with the age of the patient and the degree of involvement of the other parts of the arterial channel by the disease process. Alas the more distal the part grafted the less likely is the attempt to succeed. Grafting or thrombendarterectomy below the inguinal ligament is seldom successful. The best way of dealing with a primary channel which has been occluded by an embolus is of course embolectomy[6,7]. It should be employed whenever feasible and as early as possible after embolization. As a rule six to eight hours are considered the latest for surgery to be performed. However instances of successful embolectomy after a lapse of a considerably longer period of time have been reported[8]. For technical considerations the reader is referred to textbooks of surgery. In the case of thrombotic arterial occlusions interfering with blood flow to the lower extremities the results of radical surgery—arterectomy with vessel grafting[9,10] in some cases perhaps also with intimal stripping[11,13]—are very encouraging providing one is dealing with not too extensive a thrombus in a large vessel[14,16]. The best results have been described in saddle thrombi of the aorta (occlusions right above the bifurcation often called Leriche Syndrome). Technics are described in the surgical literature quoted. While several years ago arterial resection was at times considered an adjunct to sympathectomy[1] most surgeons by now have abandoned sympathectomy as an adjunct to removal of the thrombosed arterial segment. Very interesting experimental as well as clinical investigation has been and is being carried out concerning the type preservation use and securing of grafts to bridge vascular defects[4]. For detail the reader is referred to the abundant surgical literature on the topic.

Chapter 2 Enhancement of Secondary (Collateral) Arterial Blood Supply

MEDICAL MEANS

The therapeutic usefulness of such measures as are mentioned above is by no means restricted to their effects on the primary arterial channel. Their main value lies in their ability to aid in the activation of secondary (collateral) channels. This purpose, of course, calls for repeated and prolonged employment of the therapeutic measures available.

Medical means to enhance collateral circulation are directed not only at lessening vasomotor tone but, even more important, at fencing off further vasoconstrictor impulses to the area. The basic principles of a "peripheral vascular routine," which have been fairly generally accepted, are the best example for the application of the above on a broad conservative basis. The following routine measures are frequently utilized:

1. Keep extremities dry and warm.
2. Avoid injuries. If such occur, report immediately to the doctor.
3. Use wide, firm shoes allowing for as many pairs of woolen socks as necessary.
4. *Do not smoke.*
5. Take three ounces of Scotch, Bourbon or brandy.

It should be noted that an important point in such routine measures is to shield carefully the afflicted part against injury of any kind. That should be also understood to exclude the use of local heat and of all local physiotherapeutic procedures[6] except body warming for reflex vasodilatation and graded exercise.[7, 8] If used early enough, for example in young diabetics,[9] such routine is probably the best means to prevent situations necessitating more radical specific treatment. To this preventive routine two more measures should be added: a. Heating of the body (and nonaffected extremities) to induce reflex vasodilation (therapeutic application of the Gibbon-Landis procedure). It is necessary to apply this procedure daily for a prolonged period of time. b. Carefully graded exercise under supervision. This is done according to a flexible plan; quantitation of daily increments are based on repeated clinical evaluation. Both measures are not only capable of increasing blood supply to the extremity but are capable also of improving the vasomotor responses in the limb.[30]

For patients incapable of walking, graded exercise may conveniently take the form of the well known "Buerger's Exercise."[31] These are done daily for about a half hour, and the following sequence is recommended: The patient, lying on his back, first places his feet on a support that provides an elevation of about 25 cm. (6.7 in.) for one minute and flexes his toes and feet rhythmically; following that he sits up at the edge of the bed and dangles his feet for one minute. One minute of rest in the horizontal position completes the cycle. This should be repeated up to ten times according to the patient's general status and his reactions. As a rule, patients with occlusive *arterial disease experience pain either on elevation alone* or on elevation plus exercise. Except for the time of exercise, it is advisable to permit these patients dependency of the affected limbs to about 5-10 cm. below the horizontal for at least a few hours each day, unless edema formation prohibits this. For patients whose general status (chronic congestive heart failure, severe chronic pulmonary failure, extensive ulcerations, debilitations, etc.) excludes even the use of Buerger's exercises, the Saunders vaso-oscillating bed, which replaces the active exercise with rhythmically induced changes of blood volume and hydrostatic pressure conditions in the extremities, may be used.

Since the time that Landis and Gibbon published their interesting idea of applying alter

nate suction and pressure to enhance circulation in the lower extremities[3] various physiotherapeutic apparatus have been marketed for the treatment of occlusive peripheral arterial disease In general all the e apparatus use the principle of alternating ischemia and hyperemia[33] the danger of further damaging the hypoxic tissues during the i chemia phase outweighs the possible benefit[34] from passive exerci e and reactive hyperemia

Since 1923[3] fever therapy especially intravenous typhoid vaccine has been u ed in various peripheral manifestations of vascular di ea e Fever therapy has also been used at times to influence the course of occlusive peripheral arterial disease[35] This type of treatment was based on the rationale that the re pon e to pyrogens includes delayed and long lasting wide pread va odilation after the chill It seems however that this phenomenon applies to vi ceral organs (especially the kidneys) rather than to the extremities Thus its u e has been revived for the treatment of hypertension[37] but its value in obliterative arteriosclerosis and obliterative thromboangiitis[38,39] is doubtful to say the least In end arteritide of unknown etiology including temporal arteritis evaluation is extremely difficult because of the self limited course of the e conditions Acute arteritides for example are mostly accompanied by fever

There has been an increasing tendency to try to increase collateral arterial blood supply through the u e of various drugs usually designated as vasodilators The e drugs belong to different chemical and pharmacologic groups their modes and places of action differ accordingly When di cussing the u e and usefulness of this variety of drugs grouping according to more than one criterion appears neces ary

Of the agents u ed in the past some have never been proven by physiologic methods to have any measurable influence upon blood flow to the extremities among these are the various pancreatic and other tissue extracts hypertonic aline and aminophylline

In recent years many drugs capable of inducing vasodilation in various va cular beds have been developed The reports on their pharmacologic qualities have stimulated renewed intere t in the possibilities of medicinal treatment of hypertensive di ease as well as of peripheral va cular disease Several of these drugs are valuable in both conditions

It appears convenient to class drugs that affect extremity blood flow according to their mea urable physiologic actions in man This allows for a more detailed classification according to pharmacologic chemistry within the groups so e tablished The mechanism of action is the most difficult criterion to use in classification for some drugs work through more than one mechanism using more than one type of pathway and some of these mechanisms are fairly well described while others are largely unknown Thus we may differentiate three groups

1 Drugs with a predominant effect on blush areas expressed in surface temperature changes

2 Drugs with a predominant effect on glomus areas expres ed in surface temperature changes

3 Drugs with a predominant effect on blood flow to the extremities as measured by plethysmography and surface temperature changes

Group 1

Histamine This has been described as a capillary vasodilator It is capable of producing Lewis triple respon e in the skin in minimal amounts 0 025 mg of base by vein produces dilatation in the blush areas without affecting the glomus areas Side effects—substernal oppression shortness of breath burning of kin—are somewhat less marked when the drug is given intra arterially in doses of 3 mg in 500 cc of saline at a rate of 3 drops per beat[40] Even so side effects are almost invariably sufficiently marked to enforce a temporary slowdown of rate of administration There is a significant but short lived increase in blood flow to the extremity which returns

to resting values after a few minutes, effect *upon the blush areas by far outlasts the increase* in blood flow

Nicotinic acid This is one of the oldest peripheral vasodilators Orally as well as parenterally it causes marked dilatation in the blush areas with very marked tachyphylaxis

Roniacol (3 pyridine methanol or β pyridyl carbinol) *This is the alcohol corresponding to nicotinic acid* to which in the body it is slowly converted [41] Its pharmacologic action is essentially that of nicotinic acid but prolonged through the low release The dose is 300 600 mg divided into four daily doses Its usefulness in regulatory disorders of the *minute circulation (chronic trench foot and* the like[4]) is better established than that in occlusive vascular disease[43 44]

Papaverine has enjoyed some reputation as an agent capable of influencing cerebral circulation [4] In the periphery intravenous as well as intra arterial administration of doses from 75 150 mg are followed by vasodilation in the blush areas shortness of breath chest pain and coughing spells

Group 2

Ethyl alcohol taken orally is probably the oldest and most widely used vasodilator In single large doses (100 cc) it affects the blush areas irregularly (it may either cause dilation or constriction there) but invariably causes marked increase in glomus area temperature Used intravenously in the form of diethylaminoethanol (1 mg in 50 cc of water) it produces marked increase in blood flow to the extremity Procaine which has some vasodilator activity [45] metabolizes to paraminobenzoic acid and diethylaminoethanol Paraminobenzoic acid has no vasodilator qualities so that any such action of procaine must be attributed to the diethylaminoethanol component

Nitroglycerine and sodium nitrate have known vasodilator qualities [45] The peculiar influence of sodium nitrate on the peripheral circulation has been elucidated to a great extent by Soma Weiss and Robert W Wilkins [47 48] *who showed the dependency of its vasomotive* effects on posture In their end effect upon the extremities the nitrites cannot be classed as vasodilators because they either do not influence blood flow at all or diminish it [49]

Group 3

Numerous drugs have been developed recently on a more physiologically specific basis Most of these drugs exert their vasodilating action either by interfering with circulating catecholamines (antiadrenergic or adrenolytic drugs) or by action, possibly, on the vasomotor centers in the central nervous system *many of them are valuable in the treatment* of arterial hypertension as well as arterial disease of the extremities Some of them exert their action by more than one mechanism

a Drugs with predominantly antiadrenergic action

Dibenamine (N,N dibenzyl β chlorethyl *amine)* [50 1] *This is the mother substance of* adrenolytic (adrenergic blocking) agents in common use *It can be administered parenterally only because of its high peroral toxicity* furthermore its hypotensive effect is so marked and sustained that it is not of practical use in peripheral arterial disease *Dibenzyline (N phenoxy isopropyl N benzyl β chlorethyl amine hydrochloride)* which can be used orally is closely related to Dibenamine, but is five to ten times more effective[5] and much less toxic [3] The dosage varies considerably from subject to subject in respect to the production of adrenergic blockade and to tolerability [1] It ranges from 10 300 mg with an *average of 60 180 mg daily administered in* divided doses The side effects are essentially due to excessive adrenergic blockade The drug is rather slowly metabolized evidence of adrenergic blockade may be present as long as 2 to 3 weeks after discontinuation [54 6]

Ilidar (6 Allyl 6 7 dihydro 5H dibenzarepine phosphate)[57] is very similar in its action to Dibenzyline It also shares essentially its indications side effects and contraindica

tions It is given preferably by mouth daily doses of 50 250 mg

Ben odioxane an adrenolytic agent has been u ed for the detection of pheochromocy toma [5] It has not been used in peripheral vas cular di ease becau e of its marked hypoten sive action and the potential dangers from it

Regitine (2 N p tolyl N m oxyphenyl ami nomethyl 2 imidazoline) also called phentola mine is a strongly adrenolytic weakly sympa tholitic agent Its action is very short lived in man hypoten ion is pronounced and it is im practical for use in peripheral arterial diseases although it increases blood flow to the extremi ties It is however considered at present the best screening drug for the detection of pheo chromocytoma [9, 61]

Priscoline (2 benzyl 4 5 imidazoline hy drochloride tolazoline hydrochloride) is a par tially sympatholytic and pos ibly weakly ad renolytic agent with an alleged direct action on the vessel wall It has been given intra ar terially[6] in doses of 10 20 mg every 6 hours It may be given intravenously in the same man ner or orally in doses of 25 50 mg every 4 hours [63] It is said to dilate muscle ves els as well as skin vessels but we have not been able to verify this by plethysmographic measure ments Hypotension is not a problem The sys temic side effects [64] mainly burning of the skin are marked also with intra arterial use provid ing the dose is large enough to increa e urface temperature This is due to the fact that the blush areas markedly participate in the re sponse We have repeatedly observed leg pain immediately following one intra arterial or in travenous administration of a ingle large do e (75 100 mg) this appears to be due to a de crea e in mu cle flow that occurs parallel with increase in kin flow On the other hand there may be prompt relief of pain in i chemic ulcers followed by slow healing [63]

b Drugs with predominantly ganglionic blocking action

Tetraethylammonium chloride (Etamon) is a sympathetic ganglionic blocking agent with very little parasympathetic effect [63] Because of marked postural hypotension it is not recom mended for therapeutic u e in occlusive pe ripheral arterial disea e It also has been dem onstrated to show decrea e in blood flow to the sympathectomized extremity [66] It may how ever be u ed in the diagnosis and evaluation of arterial spasm

Hexamethonium (hexamethylene bis tri methylammonium chloride) Methium (oral) Hexameton (parenteral and oral) In contrast to tetraethylammonium this drug in addition to its marked sympathetic blocking effects has also marked parasympathetic blocking action The e undesirable ide effects include con ti pation (sometimes leading to paralytic ileus) bladder atonia (cholinergic urinary retention) and inhibition of gastric secretion [67] Such side effects and the marked hypotension and to a lesser degree impotence after prolonged u e have cau ed difficulties even in the treatment of hypertension [68, 69] On prolonged use there is marked tachyphylaxis 1 25 mg to 100 mg are the parenteral do es given 2 or 3 times in 24 hours 125 mg to as much as 750 mg 4 times in 24 hours are u ed in oral administra tion Great caution is nece sary in the pres ence of coronary disea e Cerebrovascular ac cidents congestive heart failure and uremia may occur following sudden withdrawal of the drug Excessive hypotension is counteracted by vasopres or drugs parasympatholytic ef fects by Urecholine or neostigmine Hexame thonium is a potent peripheral vasodilator and has al o been used in peripheral arterial dis ease [70] the aforementioned untoward side ef fects however limit its use in this indication to acute emergencies

Pentolpyrrolidinium (1 methyl pyrrolidi nium bitartrate Ansolysen pentolinium) This compound is more predictable in oral use has le s cholinergic blocking effects than Hexame thonium and is about five times as potent[71] in producing sympathetic ganglionic blockage Its use in the treatment of hypertension is es tabli hed [7] [3] while it has hardly pa sed be yond suggestion in peripheral arterial disease

Mecamylamine hydrochloride (mecamyla

min Inversin) is a newly developed ganglionic blocking agent that is not a quaternary ammonium compound but a secondary amine It is said to be well absorbed orally and to exhibit little anticholinergic and no adrenolytic action Its reported peculiar influence upon the vascular actions of epinephrine, histamine and serotonin sounds interesting It merits further experimental and clinical work up

Ecolid (SU 3088 1 5 6 7 tetrachloro 2 2 dimethylaminoethyl isoindoline dimethylchloride chlorisondamine) This recently developed ganglionic blocking agent[74] is capable of lowering arterial pressure and has the same side effects as the other biquarternary amines but to a lesser degree[7] Studies in man concerning effect upon blood flow to the extremities are not available at the time of this writing Preliminary experiments in the dog however make it appear unlikely that Ecolid should be proven to be a good peripheral vasodilator Peripheral resistance in the femoral bed showed a short lived initial decrease followed by increase above pre experimental level in response to the drug

c Drugs with predominant action on the vasomotor centers

Hydergine is a mixture of dihydroergocornine dihydroergochristine and dihydroergokryptine While ergotamine has been known to act as a vasoconstrictor in some vascular beds including those of the extremities[4, 76] the hydrogenated alkaloids of ergot are capable of depressing constrictor tonus by inhibition of the vasomotor centers They are also said to exert a weak adrenolytic action[77, 8] They have been used in hypertension as well as in peripheral arterial disease[78, 8] Reports have been somewhat contradictory The dosage is 0 5 mg 3 to 4 times a day by either the intramuscular the oral or the sublingual route

Veratrum viride and album and the various preparations derived from it are likewise predominantly centrally acting vasodilators[83] They have their established place in the treatment of hypertension but have not been used to any extent in peripheral vascular disease although they are capable of significantly increasing blood flow to the extremities[84, 85]

d Drugs in which the mechanism and the sites of action are still uncertain

Apresoline (1 hydrazinophthalazine) is capable of lowering arterial pressure in man[86] It has a central action, but probably also directly affects the vessel wall[87] Vasomotor responses are influenced in an intriguing fashion[88, 89] It is the only hypotensive agent we have tested which does not increase blood flow *to the extremities except after sympathectomy* in normally innervated limbs blood flow sometimes even decreases after the administration of Apresoline[59, 87]

27 VI (thiophosphoric ester of 3 hydroxyphenyltrimethyl ammonium iodide trihydrate) The site of action of this drug is undetermined It is said to be neither sympatholytic or ganglionic blocking that it has no parasympathomimetic action and that it does not release histamine This information further states that one worker found marked increase in blood flow to the deeper tissues but *not to the skin in response to intravenous in*jection another worker obtained satisfactory clinical response with intra arterial administration of 10 20 mg in physiologic saline We have not been able to obtain any significant increase in blood flow to the extremities in response to single intra arterial doses of 10 20 mg

Arlidine (1 p hydroxyphenyl 2 1 methyl 3 phenylpropylaminopropanol) is introduced as a vasodilator of the adrenaline ephedrine series It is said to increase cardiac output and coronary flow[90] as well as muscle blood flow[91] Good clinical results in intermittent claudication have been reported[92] doses used range from 6 24 mg orally 4 times a day

When considering the mode of administration of these drugs we have to differentiate between the acute and the chronically progressive occlusion

In *acute occlusion* whenever there is any reasonable hope to restore primary circulation

through a surgical procedure this should be attempted. Where such hope does not seem reasonably founded, the use of measures to induce reflex vasodilatation should be tried. Diethylaminoethanol, the vasoactive component of procaine, is an injectable alcohol that has been effective in our hands in this indication without producing postural hypotension. It is given every 4-6 hours intravenously in doses of 1 Gm diluted in 60 ml of water. Its mode of action in producing vasodilatation is not known.

Of the ganglionic blocking agents, hexamethonium is very effective in doses of 10-25 mg intravenously. It invariably leads to increase in blood flow to the lower extremities.[8] This beneficial effect is frequently offset by sudden severe hypotension which makes its use quite risky, especially in patients with generalized atherosclerosis. Similar considerations apply to the use of pentolinium (Ansolysen) in doses of 2-3½ mg intravenously.

Tetraethylammonium chloride, on the other hand, rarely produces significant lowering of resting arterial pressure but usually does produce marked postural hypotension. Its ability to increase peripheral blood flow is inferior to that of hexamethonium, pentolinium and diethylaminoethanol. If used intravenously, 5-7 mg per Kg body weight is given.

Intra-arterial administration of histamine, Priscoline, 27 MI and other drugs has been advocated. In our hands results have not been encouraging.

The chronically progressive type of occlusion is by far more frequent. Here measures which can be applied continuously for many months and years and which interfere as little as possible with the patient's activities are obviously desirable. These requirements are actually met by oral preparations only, especially by those which have a slow rate of excretion and where a quasi-permanent effect may be achieved with a "round the clock" arrangement of administration without too frequent interruptions of the patient's day or night. Such applies, for example, to the Dibenamine derivatives. To use repeated intra-arterial or intravenous injections for any prolonged period of time is obviously impractical. Intramuscular injections may be given by the patient himself or a member of his family; even then they mean a considerable disruption of everyday living.

The various drugs used to produce peripheral vasodilation have different sites of action. Priscoline, for example, dilates skin vessels in both the glomus and blush areas for a short time, while Dibenzyline has a marked and lasting effect on the glomus areas and none on the blush area.[43] Tetraethylammonium chloride may, under circumstances, increase surface temperature in glomus areas of the skin and decrease muscle flow at the same time;[66,93] exactly the same has been observed when Priscoline was given in a single intra-arterial or intravenous dose. Careful study of the specific situation on hand aids in selecting the proper drug and continued observation indicates necessary changes in the therapeutic plan.

The theoretical argument that the vasodilatation produced is "generalized" and therefore bound to divert blood from the needing parts, thus defeating the therapeutic purpose,[94] sounds very reasonable. However, studies by several groups of investigators indicate that the responses of various vascular beds are autonomous and specific; it is known that wherever a vasodilator response can be elicited at all, its magnitude is inversely proportional to resting blood flow (the smaller the initial flow, the bigger the response), and that spontaneous efforts of the organism at developing collateral circulation, which we are attempting to enhance by cutting off vasoconstrictor impulses, take place just where primary channels have been occluded. We have been impressed by the effectiveness of agents of the Dibenamine group that are capable of blocking adrenergic impulses at the vessel wall, possibly at the terminal points of chemical transmission, the neurovascular synapse.[5]

Two oral adrenergic blockers that have been marketed are Dibenzyline and Ilidar. Dose requirements vary considerably from individual

to individual ranging from 30-300 mg for Dibenzyline and from 75-250 mg for Ilidar. Adrenergic blocking agents have marked physiologic effects and are consequently far from innocuous.

Of the undesirable side effects encountered some may be explained by excess physiologic action while others must be attributed to toxicity of the drug for the individual patient.

(1) *Respiratory tract*. Dryness of the throat and stuffiness of nose, unavoidable when blockage is effective, never constitute a reason for discontinuation of medication; occasionally if they are very annoying reduction in dose may be necessary. Bronchial asthma or any disorder predisposing bronchial spasm represents a clear contraindication to the use of adrenergic blocking agent.

(2) *Cardiovascular system*. Tachycardia is a commonly encountered effect on adrenergic blockage. Its mechanism is unexplained. Speculation and consequent experimental approach may take two main directions: (a) the tachycardia could be related to decreased coronary blood flow; (b) it might be related to the specific avidity of the heart muscle to absorb and store epinephrine and norepinephrine.[9] Clinically, the tachycardia caused by adrenergic blocking agents often decreases during prolonged administration; it is successfully counteracted by the simultaneous administration of Rauwolfia serpentina preparations and hardly ever necessitates discontinuation of medication. The presence of arrhythmias including auricular fibrillation is not an absolute contraindication to the use of adrenergic blocking agents, but calls for increased caution in dosage and very close observation. Marked drops in resting arterial pressure are very rare in response to adrenergic blockade; postural hypotension however may become a problem.

(3) *Central nervous system*. Drowsiness occur not infrequently, especially in the elderly patient. Its mechanism is not clear though it is assumed to be related to changes in blood distribution within the vascular system. Remarkable adaptation usually takes place in prolonged medication so that discontinuation for this reason only rarely becomes necessary.

(4) *Genito-urinary tract*. The occurrence of erection and orgasm without ejaculation has been reported by most of the male patients in the younger age groups. The explanation is, *in all probability*, the mechanism described by Hotchkiss[16] whereby the completely autonomously innervated external sphincter does not permit ejaculation while the internal sphincter, which is innervated in part by cerebro-spinal fibers, permits escape of the ejaculate into the bladder.

(5) *Gastrointestinal tract*. Nausea, diarrhea and occasionally vomiting may occur.

The occurrence of true intolerance is small (not more than 1%). Most patients who experience early intolerance may do well after initial reduction of dose with very gradual increase. A patient may not tolerate one adrenergic blocking agent and may tolerate another well.

SURGICAL MEANS

The idea that resection of a diseased part of an artery (arteriectomy) may relieve vasospasm in collateral vessels and improve circulation distal to the segment was first expressed by Leriche.[97] Use of this procedure in traumatic surgery has been reported.

Surgical procedures designed to enhance the development of collateral circulation have been aiming at interruption of sympathetic pathways. Nerves have been blocked with anesthetics or alcohol for diagnostic and therapeutic purposes. Accordingly such injections have been employed where it is desired to temporarily block sympathetic ganglia and nerve. The block is applied at the stellate ganglion for sympathetic denervation of the upper extremities and at the lumbar ganglia for the lower extremities. Various anesthetic drugs that have been used include procaine hydrochloride (Novocaine or Neocaine), Metycaine Hydrochloride (Neothesine or piperocaine), Monocaine Formate, Intracaine Hydrochlo-

ride Apothe ene Hydrochloride Xylocaine Hydrochloride (lidocaine) hexylcaine (Cyclaine Hydrochloride) and piperthocaine (Lucaine Hydrochloride)[98,100] The effects of the injection may la t from one hour to several days depending on the drug used and the individual s susceptibility to it

Absolute alcohol[101] 6% phenol in water benzyl alcohol and Bromsalt ol are used when it is desired to produce prolonged blockade lasting for one to six months or longer These agents destroy nerve tissue by their sclerosing action The sclero ed nerve tissue that undergoes Wallerian degeneration regenerates after varying period of time An objectionable feature of alcohol injections is a painful neuritis that frequently follows its u e and is attributed to the fibrosis it induces

The stellate ganglion (a fusion of the inferior cervical and first thoracic ganglia) located behind the vertebral artery in the space between the transverse process of the eventh cervical vertebra and the neck of the first rib is subjected to blockade in order to relieve vasospastic conditions of the upper extremities head and face For the various approaches and technics the reader is referred to excellent descriptions on the subject in texts[98] Adequate blockade is indicated by the production of Horner s syndrome (miosis ptosis of the upper eyelids and light elevation of the lower lid enophthalmos conjunctival injection anhidrosis on the face and arm and increase of surface temperature) on the injected side

Paravertebral block of the lumbar sympathetic ganglia is done for temporary relief of vasospastic conditions of the lower extremities The lumbar sympathetic ganglia lie on the anterolateral surfaces of the bodies of the corre ponding lumbar vertebrae A generally accepted technic is to introduce the anesthetic agent by a posterior route usually at the site of the econd lumbar sympathetic ganglion This produces blackade of the L_{1-4} ganglia due to the diffusion of the drug upward and downward along the fascial plane For details the reader is referred to texts on anesthesia Adequate blockade is indicated by the production of warmth flu hing and anhidrosis over the lower extremity on the injected side As far back a 1917 Leriche[13] tried to interrupt sympathetic pathways to a limb by stripping the main arterial trunk supplying it Effects of this removal of the sympathetic periarterial plexus were very short lived Nowadays preganglionic sympathectomy has replaced this and other po tganglionic procedures

For sympathetic denervation of the upper extremity the stellate ganglion (fused superior cervical and first thoracic ganglia) and the second thoracic ganglion are removed This may be done by an anterior[103] or a po terior approach[104,10] and the reader is referred to textbooks of surgery and neurosurgery for the various technics employed

Interruption of the sympathetic innervation of the lower extremity is accomplished by resection of the fir t econd and third lumbar paravertebral ganglia These ganglia are accessible through an anterior transperitoneal route[103,110] a posterior retroperitoneal approach[111] and most popular lately through an anterior extraperitoneal procedure[109,11,113]

Interruption of sympathetic pathways to a limb is as a rule followed immediately by a palpable increase in warmth and a visible reddening and striking dryne s of the skin These clinical ob ervations together with marked increase in surface temperature led to understandable enthusiasm for sympathectomy

In the election of patients for sympathectomy various factors are taken into consideration Patients over 60 years are poor subjects for the operation Patients whose difficulty is exclusively intermittent claudication do not stand to obtain any benefits from the procedure In such cases however where the occlusion is high (e g iliac or high femoral) or where there are evidences of impending gangrene in the di tal part of the extremity sympathectomy is believed to be ju tified by ome surgeons[114,11] Other workers believe that the operation is mo t useful when the arterial ob truction is di tal indications include the pre ence of a small nonhealing ulcer small localized gangrene limited to part of a toe rest

pain and what the authors feel to be its precursors namely coldness and paresthesia

There is a difference of opinion as to the benefits derived from sympathectomy Some surgeons use it only as a prophylactic measure in two types of cases 1 where there is clinically obvious sympathectic hyperactivity 2 where a potentially hazardous situation with respect to the arterial supply may arise during or shortly after grafting These surgeons find that intermittent claudication localized ulceration and rest pain are seldom significantly favored by the procedure nor does its earlier performance contribute to the success of local amputation in the foot [116] It appears that such prophylactic preparation of the patient may be accomplished to at least the same degree by pharmacologically inducing adrenergic blockade

As clinical use became widespread disappointing experiences due to lack of improvement or relapse after initial relief became more frequent A considerable body of physiologic investigation has accumulated which helps to understand the above mentioned course of events (See Part I)

The adequacy or completeness of sympathetic denervation to a part is gauged by elevation of the surface temperature a visible flush and abolition of sweating in the part Where such changes do not occur their production by a paravertebral block or spinal anesthesia confirms the inadequacy of the operation These tests have been in use for a long time It appears however that a more elaborate somewhat cumbersome procedure may be more reliable in ascertaining the completeness of denervation achieved This procedure consists essentially of measuring the responses of the denervated limb to vasomotor stimuli It is an established fact that sympathetic denervation is followed by marked alteration of vasomotor responses

Crushing of somatic nerves carrying cutaneous sensation to the area has been found to offer some relief in certain cases of Buerger s disease with excruciatingly painful lesions The nerves subjected to the procedure are the superficial and deep peroneal the posterior tibial the sural and the saphenous nerves [117]

The management of functional arteriospastic conditions calls for little further explanation Whenever the cause can be found and removed such as in the cervical rib or Scalenus Anticus syndrome the treatment is of course surgical [118, 1] Medical means to lessen vasoconstrictor tonus may be used freely

Raynaud s disease seems best managed with sympathectomy followed by the prolonged peroral use of adrenergic blocking agent

In erythralgia the only serious though rare vasodilator type of regulatory disturbance Aspirin and cool environment are still the best one has to offer

Chapter 3 Management of Impairment of Venous Drainage

MEDICAL MEANS

1 Disturbances in deep venous channels Phlebitis and venous thrombosis are closely related and almost invariably appear as one disease process [1,2,3,4] It appears that occasionally the inflammatory component can be promptly alleviated by use of the anti inflammatory agent phenylbutazone (Butazolidine) [1] It is recommended that in the early acute state especially in the idiopathic case *600 mg of phenylbutazone be given on two* successive days If improvement is not dramatic the attempt should be considered a failure and discontinued If there is marked remission of pain redness and swelling within 24-48 hours the dose may be cut to 300 mg and medication continued for one week Patients treated with phenylbutazone must be checked daily for fluid retention blood counts should be done repeatedly to detect early the rare occurrence of bone marrow depression Antibiotics may be given if systemic reaction warrants their use

The time honored procedure of resting the involved limb in an elevated position still has a place in the treatment of acute venous thrombosis There is a growing tendency to mobilize *the patient as early as possible under the pro*tection of anticoagulants and with the use of elastic bandages or a Unnaboot

The aspect of treatment of deep venous thrombosis has changed radically with the advent of oral anticoagulants and the development of well workable regimens incorporating the use of both the parenteral (heparin) type and the oral (coumarin) type of drug

The main reasons why anticoagulant therapy has become the first choice of most workers in the field and of the overwhelming majority of the medical public seem to be 1 General recognition of the fact that thromboembolic disease is a systemic rather than a localized condition It thus appears logical that ligation of selected vessels cannot be considered a measure preventing further thrombus formation in other places hence it cannot be considered to any large degree a safeguard against the occurrence of embolic phenomena It may however be well argued that most pulmonary emboli stem from thrombi in the lower extremities so that for *example ligation of the vena cava inferior* may be considered a rather formidable preventive measure [1,3] 2 The indisputable evidence that the use of anticoagulants has significantly decreased the mortality rate from pulmonary embolization due to venous thrombosis [1,8,129]

There are two types of anticoagulant drugs available the heparin type and the coumarin type

Drugs of the heparin type have a marked effect on whole blood clotting time Their action while chiefly antithrombic is to a much lesser degree also antiprothrombic and antithromboplastic [1-3] They are administered intravenously or intramuscularly Determination of clotting time is simple but unpredictable fluctuations are troublesome especially with the intramuscular use The latter mode of administration is also quite painful Two syn*thetic heparin like compounds have been tried* Treburon[130] and Paritol[131] Both produce marked allergic reactions in a high percentage of cases [132,133]

The clinical usefulness of heparidin[134] remains to be ascertained Intravenous trypsin is not recommended for the considerable hazards connected with its use [135]

The coumarin type anticoagulants are in general taken by the oral route there are some *preparations permitting intravenous use Their* action is mainly upon prothrombin activity measurement of prothrombin time is therefore used as guide in their clinical administration Although the increase in knowledge of details concerning the clotting mechanism of the blood has been followed by an increase in

known details about the specific actions of several of the coumarin type anticoagulants the method of checking on their effect has remained essentially the same Prothrombin may be expressed in percentage of prothrombin concentration The latter is assumed to be normal (100%) when the prothrombin time is 12 seconds[136, 137] The therapeutic range is said to be between 10% and 30% of normal We should not overlook the justifiable criticism which points out the confusion caused mainly by the variety of methods used in the per cent manipulation[1, 3, 138] It is recommended that prothrombin activity be expressed in terms of prothrombin time in seconds using a thromboplastic preparation that gives prothrombin time 13 16 seconds for the normal control The therapeutic range is then between 25 35 seconds prothrombin time should not be permitted to exceed 40 second It is recommended that the same laboratory be used for follow up in any given case to keep conditions of determination constant

It is likewise recommended that parallel prothrombin time determinations be performed in diluted as well as undiluted plasma because after a dose of the anticoagulant prolongation in the undiluted plasma might be equivocal while in the diluted plasma a prolongation definitely beyond the range of the control might be apparent thus permitting better evaluation of further dosage to be used[139, 141]

It is obvious that the oral route is preferable to intravenous administration whenever treatment has to be continued for any length of time providing the orally taken preparation is well absorbed Such is the case with the coumarin type anticoagulants Their disadvantage in urgent cases is the elapse of considerable time before the first dose becomes effective This difficulty is met by using intravenous heparin simultaneously with the oral anticoagulant the latter being continued under prothrombin time control and heparin being discontinued when the oral drug has become effective The other major difficulty encountered with oral anticoagulants is that the relationship of dose to effect is largely unpredictable[1, 3, 141]

Many antiprothrombin agents have been developed since Link[1, 3] and his co workers discovered dicoumarol as the cause of hemorrhagic sweet clover disease in cattle Recently Weiner Brodie and Burns[14] published their thorough comparative study of hypoprothrombinemic agents 8 of which appear to be clinically usable Table IV which indicates the differences in dosage as well as in time of action is taken from their publication The 8 clinically usable agents are arranged in progressive sequence according to the time elapsed between administration of a single dose and the maximum effect produced in prolongation of prothrombin time

In the acute case or where there is a history of previous embolism it is advised to administer heparin intravenously about 100 mg every 1 6 hours for 24 48 hours Simultaneously an oral anticoagulant should be started If a slow acting drug (e g dicoumarol) is used intravenous heparin should be administered for 18 hours in the event a fast acting coumarin drug (e g Tromexan) is chosen heparinization may be discontinued after 24 hours

Shapiro and Weiner[1, 3] have tried to obviate the difficulties arising from the unpredictability of the prothrombin time trend by changes in the method of administration of oral anticoagulants Instead of a moderate initial dose followed by a smaller maintenance dose a large initial dose is administered Daily prothrombin time determinations will then show the peak of effect lasting for several days followed by a downward trend when this downward trend is established a smaller booster dose is given and repeated when necessary

How long anticoagulant therapy should be kept up in a given case is a question of clinical judgment Three to four weeks may be mentioned as an average for the acute case however the course of the local sequelae of thrombosis the general status of the patient and the occurrence of complications are the main mod

Table IV

Drug	Dose mg	Day of peak	Prothrombin recovery	Rate of metabolism
Tromexan	1650	1	2	25% per hour
G 23 350	20	1 2	3	
Phenylen lan dione	350	2	4	10% per hour
Dicoumarol	400	2 3	5	25% per day
Cumopyran (63)	150	2 3	5 6	
Warfarin (42)	65	2 3	5 6	17% per day
Marcoumar	21	2 3	6	
Dipaxin	20	3-4	7	

ulating influences Where the picture of chronic thrombophlebitis or the post phlebitic syndrome develops prolonged use of coumarin type anticoagulants extended for months and even years has been advocated [143 144] It is agreed among workers in the field that rigidity of laboratory control may be *relaxed in these cases for three reasons* 1 The maintenance doses used are usually comparatively small 2 The desired prothrombin time level is lower than in the acute case 3 In most patients a pattern of response to the drug develops which *is fairly constant As a rule an* individual pattern of drug administration can be established on which the prothrombin time remains within the desired range (around 30 second undiluted) Once such a pattern has been established it is sufficient to have the prothrombin time determined every 2 3 weeks

Contraindications to the use of anticoagulants are

a *Absolute*

Active bleeding of all kind *including* purpuric manifestations impaired liver function septic thrombosis and embolism blood dyscrasias (with impaired clotting) pregnancy in last trimester

b *Relative*

History of bleeding ulcers of the GI tract advanced kidney disease

*The danger inherent in anticoagulant ther*apy is bleeding Frank sometimes massive hemorrhage may occur from any organ or organ system The mechanism of its occurrence is unknown Occasionally bleeding due to coumarin drugs may occur below the safety level of 40 seconds undiluted prothrombin time and *in other cases no bleeding may occur above this* level The changes in coagulability of the blood per se certainly do not explain the occurrence of hemorrhage while they may explain of course continuation of otherwise induced bleeding

In the event bleeding occurs one of the measures to be taken is the transfusion of fresh blood This should be done in bleeding from both types of anticoagulant [1 3] In bleeding due to coumarin type drug intravenous injection of 75 mg of vitamin K or preferably 20 50 mg *of the more effective* K_1 orally or intravenously is given repeatedly if necessary [1 3 141] In bleeding due to heparin repeated injections of Protamine are indicated [144 145]

Salicylates and sulfonamides are synergistic with anticoagulants. Evidence has been shown for hemorrhagic action of salicylates[14] and for their hypoprothrombinemic effect.[147] Salicylates therefore should not be used concomitantly with anticoagulants. A synergistic action of sulfonamides with anticoagulants is less well established[1 3] but great caution is definitely advisable. The mechanism conceivably involves the destruction of bacteria normally responsible for the synthesis of vitamin K.[147] This might be true for all bactericidal therapy that is orally administered. Vitamins K and K_1 and methylated xanthines (caffein, theophyllin, theobromin) are antagonists of anticoagulants.

The influence on blood coagulation of some commonly used drugs may present difficulties in the institution of anticoagulant therapy in patients receiving these drugs. Since patients with cardiovascular diseases in whom anticoagulant therapy is contemplated may very frequently be receiving xanthine derivatives, it is well to remember the enhancing influence on blood coagulation of the purine bases. Penicillin, contrary to initial reports, does not increase coagulability of the blood.[148, 149] Evi*dence to show an influence of Digitalis upon* blood coagulation has been unconvincing.

2. Disturbance in superficial venous channels. Inflammation and thrombosis in superficial venous channels is never of alarming clinical significance except as a diagnostic cue in early obliterative thromboangiitis. In *the presence of considerable varicosities,* elevation of the foot of the bed (to insure permanent drainage throughout the night) is advised and the use of elastic bandage to restrict filling and prevent further distension of the *dilated* channels may be very helpful.

SURGICAL MEANS

1. Disturbance in deep venous channels. Venous thromboses may occur as a result of physical trauma, chemical injury (e.g., following injections), extension of infectious foci, as a complication following parturition and other pregnancy states, and after prolonged bed confinement. The veins involved may be the deep or the superficial set. Such thrombosis may heal completely with "restitutio ad integrum" or it may cause permanent obliteration of the vessel producing impair*ment of the venous drainage of the part.* As a rule this is after varying period of time compensated for to a greater or lesser degree by the development of collateral vessels which bypass the occluded segment. Where this does not happen soon enough or to an adequate degree, various signs and symptoms attributable to insufficient venous drainage become manifest in the involved part.[1 0 1 ?]

If the thrombus is friable, poorly adherent to the vessel wall with a tendency to further *propagation, a serious situation arises whereby* emboli may be thrown repeatedly into the circulation. Pulmonary embolization, if repeated or massive, may be fatal. Where the thrombosis is accompanied by marked inflammatory change, the thrombus may be firmly adherent to the vessel wall and is thus less likely to cause embolic phenomena. However, if the clot is infected, suppurative changes and liquification necrosis will cause fragmentation of the otherwise adherent thrombus and septic emboliza*tion follows, leading to pulmonary infarction* and suppurative metastases elsewhere as well as a generalized septic pyemia. There is convincing evidence that whenever serious embolic phenomena, including pulmonary infarctions, occur in thrombotic disease, they almost invariably arise from thromboses in the deep veins of the lower extremities.[1 3 1]

Conservative measures, including those designed to favor venous return flow (e.g., elevation of the involved limb), the use of anti*biotics* and *anticoagulant* therapy are employed in the management of thrombophlebitis in general. Where these measures appear contraindicated or insufficient, venous ligation *above the site of involvement, which can effec*tively prevent the embolic phenomena as well as check the spread of the process, may be resorted to.[1 6, 163] When many venous channels in a region are *involved at the same time (e.g.,* postpuerperal or postabortal septic pelvic thrombophlebitis), ligation of the inferior vena

cava is the operation of choice. Details of the surgical procedures may be obtained from textbooks on operative technic.[164]

Either preoperatively or in the event a more extensive surgical procedure of venous ligation appears contraindicated, a less radical procedure has been employed, namely *regional sympathetic block.* Stimuli arising from the thrombophlebitic segment apparently cause the excitation of vasoconstrictor impulses that are transmitted through the sympathetic fibers which in turn produce vasospasm of the involved vessel and its accompanying artery.[165-167] Sympathetic block interrupts these vasoconstrictor impulses, thus relieving the spastic state.[168, 3, 1]

2. Disturbance in superficial venous channels. *Thrombophlebitis involving superficial veins* is usually managed adequately with conservative measures, including elevation of the affected limb, the use of analgesics symptomatically, and antibiotics in the presence of infection. The application of elastic compression bandages may be beneficial in some cases. The administration of phenylbutazone in divided doses of 800 mg daily has been useful in the hands of some workers. Because of the benign course followed by superficial thrombophlebitis, the more radical measures, e.g., anticoagulant therapy and venous ligation, are as a rule not indicated.

Surgical management of varicose veins may be accomplished by two methods used singly or in combination: ligation with varying degrees of resection of the varicose vein and the injection of sclerosing solutions. The relative simplicity of the injection procedure and initial reports of good results made it very popular. *The varicose veins are obliterated by the introduction into the vein of a sclerosing solution that causes scarring and produces an adherent thrombus inside the vessel.* The solutions used include sodium morrhuate, sodium gynocardate, quinine, urethane, Monolate, and Sequals. However, sclerosing therapy, especially when used alone, has been disappointing in the long run.[17, 1, 4] Injection reactions were not infrequent, and recurrence due to redilatation of the thrombosed segment as well as recanalization *of the thrombus was rather common.*

Ligation and resection of varicose veins appears to be the operation of choice. Depending on the site of the involved vessel, the procedure is done on the long saphenous vein at the fossa ovalis as it empties into the femoral vein, or on the short saphenous vein as it drains into the popliteal vein in the popliteal space. In either case, the principal tributaries of the vein to be resected are carefully dissected, ligated, and divided. After resection, the remaining distal portion of the vein is either obliterated by a sclerosing injection or removed by stripping. The procedure may be *done with a Mayo extraluminal stripper or the* superior Myers intraluminal flexible vein stripper. The desired length of vein is stripped *from its surrounding tissues* beneath the unbroken skin with the use of the instrument, incision being done at the sites of the extremities of the removed segment.

Linton[17] called attention to the important role the communicating veins play in the persistence of varicose veins and the production of varicose ulcers. In the presence of incompetence of these veins, it is necessary that such vessels be also isolated and ligated.[1]

The treatment of chronic lymphedema has been by and large unsatisfactory. Physical measures such as elevation of the limb,[1, 6] and of the foot of the bed, and the use of elastic bandages *may be of temporary value in the early stage.* In fully developed elephantiasis or in Milroy's disease this does not offer any *relief, while surgical measures, short of radical* removal of the tissue masses,[8, 9] have not been gratifying.

Chapter 4 Therapeutic Measures Influencing Primarily the Minute Vessels

To date the search for an agent capable of demonstrably repairing damage to the capillary wall or predictably influencing capillary permeability has been in vain

Symptoms arising from regulatory disturbances in the minute circulation as seen in chronic trenchfoot may be relieved considerably with the use of pharmacologic agents of the nicotinic acid group[4] Physiotherapeutic measures especially contrast baths may also be very helpful This is done by alternate immersion of the extremity in warm (2 minutes) and cold (1 minute) water starting and ending with the hot bath[179]

Telangiectasias as a rule are better left alone Following trauma however a spider telangiectasia may spurt occasionally from the underlying arteriolar vessel This is comparatively rare occurring in about 10% of all spider telangiectasias and is best taken care of by surgical ligation Blood transfusions have to be given for the acute anemia that frequently occurs in Rendu Osler s disease (livoid hereditary hemorrhagic telangiectasis) due to bleeding lesions Whenever the bleeding lesion can be visualized cauterization sometimes followed by excision is indicated

Primary newgrowths of the vascular system are best managed only by surgical excision The treatment of hemangiomas lymphangiomas and sclerosing hemangiomas depend upon their location and symptomatology[180 181] Benign tumors which do not cause symptoms do not require treatment In the presence of symptoms or retrogressive changes x ray irradiation or surgical excision is indicated Glomus tumors[18] that are benign though extremely painful are treated by surgical excision rarely amputation of one or two phalanges may be necessary Malignant elephantiasis is very rare

For hemangiopericitomas[183] which are quite prone to become malignant and especially with such malignant tumors as hemangiosarcomas (hemangioendothelioma)[184] and lymphangiosarcomas[185] early radical operation is the only hope even then prognosis is always guarded However cases with a protracted course and survival of many years have been reported[186] Because of the multiplicity of lesions in Kaposi s sarcoma radiation is the most commonly used treatment in addition to management of the anemia and an occasional surgical excision because of local symptomatology[187 188]

Chapter 5 Management of Underlying Conditions and Complications

TREATMENT OF GENERALIZED VASCULAR DISEASE

Obliterative arteriosclerosis comprises the majority of cases presenting signs, symptoms and sequelae of peripheral arterial insufficiency. The etiology and pathogenesis of the basic disease arteriosclerosis is still largely unknown, thus making any attempts at its prevention or of its sequelae at best hypothetical. The management of the patient therefore becomes limited to a greater or lesser degree to treatment of the existing lesions. Preventive measures include keeping the body weight down, restricting the total intake of fat and keeping up a reasonable amount of noncompetitive exercise, such measures being generally accepted as wise even with advancing age. Evidence has been presented to show that exercise is a notable factor in enhancing the development of secondary arterial blood supply [31 1 9].

The use of anticoagulants in the prevention and treatment of arterial occlusion has remained a controversial subject to the date of this writing [189, 196]. It stands to reason that the basic conditions giving rise to thrombus formation vary with the structure and function of the part of the vascular tree involved. Specifically, whether there may be hope to influence occlusive disease of the peripheral arteries by anticoagulants depends largely on the question whether these drugs possess vasodilating potentialities. Suggestion in this direction has been only indirect so far [197, 198]. It will require a great deal of experimental work and much further clinical observation before a conclusive answer can be reached.

In the presence of diabetes mellitus atheromatosis and arteriosclerosis tend to run a more fulminating course than in the average nondiabetic subject. The duration of the disease, obesity and hypertension are influencing factors [199, 0]. Possibly the age of onset and hereditary aspects are of importance [03, 204].

Contrary to some reports there is convincing evidence that excellent control of diabetes significantly reduces the incidence of vascular complications [0 03]. It may well be that the difficulties in achieving really excellent control of the diabetes encountered in most clinics [0] are responsible for the existing differences in opinion regarding its vascular complications. The question whether in a given case the degree of control of the diabetes bears a demonstrable relationship to the quantity and intensity of vascular complications is still unanswered [9 0]. It appears reasonable to strive for as good a control of diabetes as possible [08].

Vascular lesions found in collagen diseases have to be understood as part of the basic disturbances; not infrequently they also respond to the administration of corticosteroids. Where such lesions have advanced arterial occlusion and its sequelae, they have of course to be dealt with accordingly.

Specific arteritides and endarteritides (e g tuberculous or syphilitic) are to a certain degree amenable to specific treatment provided the lesions have not progressed to obliteration.

TREATMENT OF RELATED EXTRAVASCULAR CONDITIONS

The relations between various neurologic lesions and blood flow are manifold and intricate (Parts I and Part II). Some experimental information about the impact of vascular disease upon cerebral blood flow and in turn about the relationship of cerebral blood flow to brain metabolism has accumulated especially since Kety described his method of measuring blood flow to the brain [09 13]. Attempts have been made to influence cerebral blood flow for therapeutic purposes [14].

At least three therapeutic tools originally devised to influence blood flow to the extremities have been applied recently to cerebral vascular disease: pharmacologic vasodilation

[13, 18] anticoagulant therapy [17, 19, 0] and cervical sympathectomy [1] More investigative work and clinical experience are required before it will be possible to arrive at a conclusive evaluation

Wherever emotional factors seem to be responsible for the occurrence of vasomotor disturbances of one type or the other psychiatric help should be sought provided the vasomotor manifestations are serious or bothersome enough to warrant per se such action

The importance of proper cardiologic investigation and diagnosis in every case showing disturbance of peripheral blood flow is obvious from Part II Proper treatment of underlying heart disease is often followed by rapid clearing of peripheral manifestations

Careful hematologic work up (viz Part II) may likewise aid in the therapeutic approach It is of considerable interest though not understood at all that attempts to treat cases of essential thrombophilia with anticoagulants have failed

True vascular sensitivity to cold can be successfully treated with antihistaminic agents The response to cold described in Part II which characterizes these rare cases can be prevented or mitigated by administration of an antihistaminic before exposure

MANAGEMENT OF COMPLICATING SEQUELAE OF DISTURBANCES IN PERIPHERAL BLOOD FLOW

Arteriovenous fistula Spontaneous closure of acquired arteriovenous fistula (arteriovenous aneurysm) has been reported in rare instances [3] As a rule however surgical repair is necessary to relieve the increased load on the heart [4, 6] and to prevent local venous stasis In children increased growth of the limb supplied by the involved vessels is an additional sequela which may be forestalled by surgical closure On the other hand surgical closure of an acquired A V fistula that has existed for some time and where the circulation has already adapted to it may result in rise in both systolic and diastolic pressure and in spite of the slowing in rate [2, 6] in a marked decrease in cardiac output with consequent heart failure especially in the presence of compensated heart disease For this reason preoperative digitalization is advised

Surgical repair may be done in the rare cases of congenital A V aneurysm In the majority of cases however this is not possible due to the extent and multiplicity of the lesions One is limited to conservative measures such as the use of rubber bandages for compression of the usually abundant ectatic superficial veins and convolutes Ligation or the use of sclerosing agents are not advised [7]

In case of Paget s disease where hypervascularization has led to similar consequences as an arteriovenous fistula digitalization and other means to enhance work performance of the heart represent the only possible approach

Ischemic Ulcers and Gangrene The necrotic part is usually referred to as gangrene Where this is localized and sloughs off an ischemic ulcer results

The management of these dreaded sequelae of occlusive peripheral arterial disease calls for measures which may help to localize the necrosis to limit or prevent its further extension to promote sloughing off of necrotic tissue and to promote healing of the resulting ulcer [8]

There are no reliable figures available on the incidence of gangrenous lesions due to occlusive vascular disease nor on the frequency with which amputation of the limb had to be performed as a life saving procedure in such case Be that as it may it appears that the over all picture has changed recently while the incidence of such complications has remained about the same the indications for major amputations may be reduced considerably and limited to instances with massive or very rapidly advancing gangrenous lesions

The use of enzymes (streptokinase streptodornase) as a moist compress as a bath as a continuous slow drip or in jelly form has been shown to be very effective in removing exudates from ulcers and wounds without traumatizing normal tissue [9, 3]

With minimal surgery limited to excision of

all necrotic tissue and removal of sequestra when present and the concomitant use of the enzymes. McCarty and Tillett[33] and McCarty[34] reported very encouraging results in the management of patients with chronic refractory ulcerations of the feet due to arteriosclerosis with or without diabetes and in the presence of osteomyelitis in some cases.

In these cases the increased rate of healing and repair occurred despite the deficient blood supply which these investigators feel had remained unchanged. They ascribed the good results to increased diffusion of antibiotics both locally and from the circulation into the area of disease which was made possible by the enzymatic removal of the exudates. They also speculated that the enzymes might have released locally some specific factor of repair that are present but are inhibited by the elements of disease until the lytic effects have been accomplished.

The favorable influence of adrenergic blocking agents in cases with impaired arterial circulation has been described in the literature.[35, 36] Wertheimer, Redisch and Steele reported the marked enhancement of healing of ischemic gangrenous ulcers following the use of Dibenzyline.[37] With the plethysmographic evidence of increased blood flow which they obtained in some of these patients during the administration of the drug, these investigators attributed the favorable response observed to an improvement of the circulation. They believe that this was brought about by the blocking of the continuous afflux of adrenergic impulses to the collateral circulation in (those) limbs with grossly impaired primary circulation. They feel that these adrenergic vasoconstrictor impulses play a large role in preventing the healing of ulcers.

We have since administered adrenergic blocking agents to many patients with peripheral arterial insufficiency and complicating ischemic gangrenous ulcers in whom amputation of the limb was held inevitable by consulting surgeons. The favorable results obtained in more than half of the cases with relief of symptoms, localization of the gangrenous process, better control of the infection and surprisingly rapid healing beneath the necrotic slough is very encouraging indeed. It should be noted that a striking feature in these cases is the appearance of pink healthy granulations that replace the pale, soggy, grossly devitalized tissues at the base and edges of the ulcer. Where the gangrenous eschar has to be debrided, the readiness with which bleeding occurs offers clinical evidence of the increased blood flow in the area. In some cases peripheral pulses reappeared in the course of the administration of the adrenergic blocking agent. In the light of these observations it appears that the favorable change in the clinical course of these patients is attributable to an improvement in their vascular supply, primarily by the enhancement of the development of collateral circulation and secondarily by some improvement in the originally insufficient primary vascular channel. That reparative processes as well as higher and more effective antibiotic levels may become better available to the area under these circumstances appears to be a logical consideration.

The concomitant use of adrenergic blockers and enzymes yielded even better results in those cases where we had occasion to use them. No conclusive figures are available at the time of this writing, but it appears that a considerable increase may be attained in the percentage of limbs that can be salvaged from amputation by the combination of judicious use of adrenergic blockade with the method described by McCarty and Tillett.

The problem of secondary infection, the cause of so-called wet gangrene, has become much easier to handle since the advent of sulfa drugs and antibiotics. Whenever possible, material from the gangrene should be cultured and specific sensitivity of the pathogenic organisms determined. The chosen agent should be used systemically. With the exception of streptokinase-streptodornase, use of medicated local applications is not recommended. It is usually ineffective not only because of impaired absorption but it may even produce local maceration and irritation and thus cause further

devitalization of the tissues The extensive use of antibiotics may enhance fungal growth at the lesion a complication to be cautiously watched for Packing of the limb in ice must not be attempted as long as there is the lightest hope of saving the part Only when the decision has been made to perform (after a short delay) amputation can packing in ice be considered it diminishes the absorption of toxic substances from the necrotic parts and is quite helpful in combatting pain

Proximal amputation is indicated when the gangrene or necrotic process has progressed to involve the bone tendon or joint capsule under which circumstances spontaneous healing is unlikely The optimum level—minimum sacrifice of the limb with reasonable assurance of a healing stump—at which amputation has to be performed is best decided on the operating table The amount of bleeding observed [39] at the planes of incision and the gross appearance of the muscles [39] at the site whether pink and healthy looking or soggy and brownish serve as useful guides in determining the eventual closure or nonhealing of the operative stump

During recent years there has been a noticeably increasing tendency to sacrifice less and less of the extremity in such surgical procedure Amputation is performed as far distally as possible with the provision that the incision be done through relatively normal tissue

Details of surgical technics are readily available in standard textbooks on the subject It may be well to reiterate however as Leermooth and Sles or emphasize that in any operative procedure involving limbs where arterial insufficiency is the basic underlying pathology the minimum handling of tissue is of paramount importance In amputations performed because of vascular disease they stress the strict necessity of avoiding tourniquet the use of equal flaps the careful avoidance of constriction at the flap margins and the extreme importance of the gentle handling of tissue [40]

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Part V The Anatomic Basis of the Peripheral Circulation in Man

Or the Concept of the Macromesh and Micromesh as Illustrated by the Blood Supply of Muscle in Man

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INTRODUCTION

SINCE MUSCLE comprises approximately 42% of the total human body weight we consider the blood supply of human muscle a matter of major importance. The detailed nature and arrangement of the peripheral vessels of man here demonstrated microradiographically for the first time make it evident that much physiologic and pathologic experimentation of the past being based on inadequate anatomical knowledge of the peripheral vascular patterns must be regarded as speculation. To any thinking medical man it should be obvious that until the correct anatomic basis is introduced into the study of such vascular problems as shock, burns, and the like, pathologic and clinical deductions must suffer. An illustrated report demonstrating these hitherto invisible vascular patterns was submitted to the National Research Council of Canada in January 1955.

A review of the literature on the subject revealed that very little was known of the blood supply of muscle in man[1] and that much of the available information was based on animal experiments. Hence it was decided to work on fresh human material and by radiographic arteriography to attempt to demonstrate muscle vessels in their entirety. Initial attempts to completely inject vessels within muscle failed but further experimentation with radiopaque agents led us to conclude that only fine grain injectants containing particles as small as or smaller than the blood cells could be expected to find their way into the smallest vessels at pressures comparable to the blood pressure of man. Such injectants demonstrated the vascular patterns of human muscle and skin in a way not hitherto observed. Moreover, such pictures quickly revealed that previous descriptions of muscle vessels were both inadequate and misleading by reason of the use of coarse injectants (fig. 1).

EXPERIMENTAL PROCEDURE

During the past four years we have studied the vascular patterns in muscle in the following various ways.

1. In order to display the grosser features of the muscular vessels we injected fresh human cadavers with a contrast medium within several hours of death. A standard x-ray unit was then used to take both straight and stereoarteriograms of the intact limbs as well as the excised and isolated muscle groups. The position of all muscular vessels was recorded during the dissection and compared with the radiographic findings. A series of over 50 stereoarteriograms of this type was taken. The combined use of radiopaque injectants of small particle size and a high kilovoltage radiological technic account for the marked vascular detail obtained.

2. The study of the finer detail of the intramuscular vessels in injected and excised muscles was performed by means of microarteriographic technics. Muscle preparations were placed beneath a Philips x-ray diffraction tube

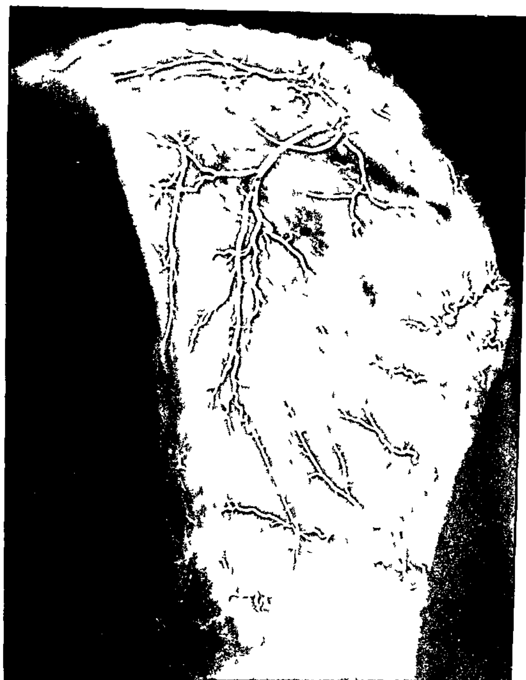


FIG 1 MUSCULOGRAM OR GROSS ARTERIOGRAM OF PECTORALIS MAJOR

This illustrates that conventional large particle injectants can reveal only the major arteries within a muscle even at high pressure The gross vessels of a right pectoral such as this are a mirror image of its left counterpart compare with the left pectoral shown in fig [illegible] even though the muscles are from different subjects Male 7[illegible] years

in order to secure the softer x rays of longer wave length and exposures were made on fine grain emulsion plate. Multiple exposures were necessary in the case of larger muscles in order to permit scrutiny and photographic reproduction of the entire intramuscular vascular bed. Enlargements of the resultant microarteriograms were then made by photomicrographic methods. Material from over 24 foetuses and 30 adult subjects has now been studied by the above two methods.

3 Microarteriographic experiments were also carried out on living animals (rat, rabbit) in order to study the microscopic vessels of living muscle and to correlate the functional behavior of these vascular patterns with those seen in man. Various muscular flaps and windows designed to minimize reactive error as much as possible[3] were used on both the trunk and limbs of these animals. The technics so evolved for microarteriography of living muscle will be the subject of a later report.[4]

4 Microcirculatory studies were also carried out on a number of animals (rat, rabbit) using the fused quartz rod method of illuminating living tissue. This served to confirm certain observations revealed by microarteriography and gave a working knowledge of the behavior of blood flow paths in living muscle under various conditions.

Similar observations were made on the peripheral circulation and arteriovenous bridges in the living human foetus.

5 Stereomicroarteriography methods developed in this laboratory[6] were also used in order (a) to study the smallest intramuscular vessels in the third dimension, (b) to remove difficulties of interpretation occasioned by the superimposition of shadows inherent in flat film radiography, and (c) to determine the volume pattern of a muscle.

EXTRAMUSCULAR ARTERIES

Little attention has been paid to the course and mode of distribution of the smaller arteries that supply the skeletal muscle of man and still less to the anastomotic connections and vascular patterns they form within the various muscles of the body. Initially our objective was the study of the intramuscular vascular patterns of man but it soon became evident that a knowledge of the extramuscular arrangement of muscle vessels was an essential corollary to an understanding of the vessels within muscle.

In view of the inadequacy of modern textbook statements we were forced both to reexamine and to redetermine the individual arterial supply of all the skeletal muscles in the human body. More recently the careful dissections of Salmon (1935) came to our attention and we were able to confirm many of his observations. The volume of material so accumulated makes it necessary to present the extra and intramuscular arrangements of the muscular vessels seriatim and to deal with only the major and clinically important trunk and extremital muscles.

Although some early work was carried out by Wollenberg (1915)[10] on the lower limb muscles, Campbell and Pennefather (1919)[8] must be credited with the first radiological study of arterial distribution in human muscle. They published a short account of their radiographic investigations into the blood supply of muscles with special reference to war surgery and drew up a classification of the limb muscles based on the number of sources of supply and anastomotic potentialities. Other than the previously mentioned work of Salmon, no further interest seems to have been shown in the subject until the conclusion of the last war when Le Gros Clark and Blomfield (1945)[1] studied the effect of gunshot wounds on the efficiency of intramuscular anastomoses in rabbit muscle. These workers appreciated the practical importance of the subject and concluded their study by stating that a knowledge of such patterns would be applicable to muscle surgery and the treatment of wounds, but that unfortunately little precise information is yet available as regards man. Following on the Power (1915),[9] Hughes (1918),[11] and Edwards (1953)[1] reported on the various clinical cases that arose from their wartime experiences



Fig 2 Musculogram of Pectoralis Major

This shows the anastomosing arterio arterial arcades which form a gross vascular network or macromesh that exists within all muscles Some of the larger veins are also visible Demonstrated by using fine particle (0 5 micron) injectants at physiological pressures immediately after death Compare with fig 1 and employ a mirror to detect the bilateral symmetry of the gross intramuscular arterial patterns in the human Female 68 years

which were illustrative of the effects of mu cle *ischaemia* they also discussed various anatom ical points that appeared to have bearing on the vulnerability of certain muscles

Anatomical textbooks give a very limited account of the blood vessels supplying muscles in almost all instances they dismiss the subject in a general manner Only the larger named muscular branches and a few muscles receive any pecific mention while for the rest little more is said than that a given artery gives off muscular branches to the adjacent muscles Gray [13] for example merely remarks that each muscle has a very rich blood supply derived *from muscular branches of neighboring arter ie* He then continues with certain incorrect observations to the effect that the e branches are inconstant in arrangement and have no communication with the blood ve sels of other structures in the neighborhood Similar state ments are made by Morris [14] although this text differs by remarking that the distribution of at least the main branches of the arteries is fairly constant o that fields of vascular supply may be mapped out Piersol[1] and Cunningham[10] also treat the subject in a limited manner

The inadequacy of textbook statement ap *pears to tem from reliance upon di ection* alone as well as from uncritical acceptance of Spalteholz s (1888) early account of the dis tribution of blood vessels in muscle (which however was almost entirely ba ed on the rab bit and the dog) While acknowledging the beauty of some of Spalteholz s cleared prepara tions of animal muscle we must not overlook the fact that he confined his tudy to isolated mu cles which may account for uch an un warranted generalization as that each mu cle is va cularly a elf contained unit Unfortunately his work was applied without qualification by subsequent writers to the human musculature Despite the cla ic nature of his work it must be held re ponsible for certain of the misunder tandings now current concerning the blood upply of muscle and its relation to urround ing ti ue

The e ential character of the vascular pat terns of human mu cle and kin would appear to have been overlooked because the dissector was apt to display only the larger vessels while the microscopist tended to concentrate his at tention on the finer terminal features of the vessels as seen in a ection However the de velopment of the previou ly described radio graphic technics have enabled us to study a larger vascular territory at one time ranging from a tissue field ½ to 5 in diameter an entire muscle or even a region of an intact limb Moreover we were able not only to image these vessel in their intact state but also to ob serve them stereoscopically

These tudies have revealed that muscular *arteries both major and minor show a quite* remarkable constancy of radiographic pattern in their extramu cular course which naturally reflects a regularity of their origin and di tri bution This is readily discerned in compar able mu cle arteriograms made on different subjects and such is the characteristic arrange ment of the major arteries lying in a given muscle that in a hort space of time the ob server comes to a sociate a certain basic pat tern with that muscle

But while both surgical experience and an atomical atlases attest to the regularity of dis *tribution*[17] *of the major named muscular ar* teries examination of a series of muscle arteri ograms impres es one with the constancy of the arrangement of many of the minor and un named arteries Such vessels have quite un derstandably been largely overlooked where re liance has been placed on dissection alone but the e smaller or segmental arteries cannot as will be seen be ignored simply because a some what larger artery appears to assume the prin cipal role for they constitute an integral part of the blood supply of that mu cle and can be demon trated with regularity

Of course minor variations in origin oc cur although many repre ent no more than dif ferences in length of arterial segments We have encountered few that appear to be of any major significance when considered from the tandpoint of the blood supply of a given mus cle or mu cle group Variations in vascular pattern naturally attend development and

growth but preoccupation with developmental irregularities[18] of larger ves els has unfortu nately cau ed many to overlook the surprising constancy of the ultimate va cular pattern of man both in respect to his major and minor ve sels Variations in origin of a principal muscular artery may in some instances con

of the given individual and surprisingly con stant from individual to individual regardless of race age or sex Moreover the e arterial patterns are established in later foetal life and agree with those observed in the adult muscu lature (cf figs 3 and 4) it is instructive to compare such vascular patterns in muscles such

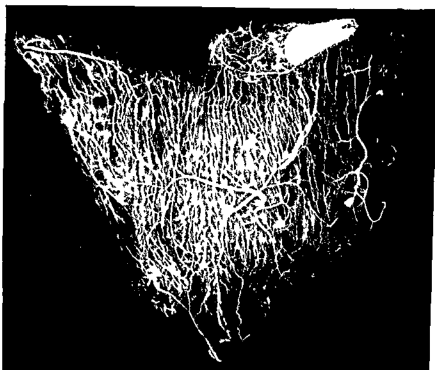


FIG 3 MUSCULOGRAM OF FOETAL DELTOID MUSCLE

Compare the va cular network within this fo tal mu cle with that of th adult d ltoid (fig 4) The e intramus ular patterns are establi hed in later foetal life Foetus C R 21 8 cm Age 6 month

ceivably determine muscular reaction to ar terial occlusion but this is only likely to apply to such muscles as fall within Class 1 of our classification (see below)

Arterial distribution to skeletal muscle i *in general the same on* both sides of the human body with the re ult that the vascular pattern observed in a mu cle (e g the right pectoral) is almost a mirror image of its left counterpart (*cf figs* 1 *and* 2) Using the methods de cribed above it has been determined that all the skele tal mu cles exhibit a characteri tic arterial pat tern that is bilaterally symmetrical in the body

as the deltoid trapezius or greater pectoral It may be assumed that there is a genetic ba is for these vascular patterns of muscle but this should probably occasion no more surpri e than the recognition that similar factors deter mine the ultimate form of the heart Briefly it would appear that the development of the e arterial patterns in mu cle have been ignored in favor of the study of larger vessels

Our radiographic studies revealed that the muscles of the trunk and limbs are generally supplied by segmental arteries which ari e either from the main arterial axes or their



FIG 4 MUSCULOGRAM OF ADULT DELTOID MUSCLE

Compare the intramuscular vascular pattern with that of the foetal deltoid (fig 3) Male 17 years

major named or unnamed muscular branches (fig 5) Such segmental arteries usually range from 1 mm to 3 mm in caliber and are so numerous (but regular) in arrangement and similar in caliber in different muscles that the idea of a haphazard supply can be discounted

The length of these segmental branches naturally varies but it seems to be related to function For example comparison may be made between the short extramuscular course of the segmental arteries passing to the long fleshy attachments of the extensor muscles of the leg and the long segmental arteries that supply the freely moving superficial flexors of the forearm This segmental pattern is immediately obvious in certain muscles (e g tibialis anterior leg extensors) where a ladderlike series of small segmental arteries can be seen passing to supply succeeding areas or segments of these muscle (fig 6) Such segmental arteries be



FIG 5 MUSCULOGRAM OR CROSS ARTERIOGRAM OF AN EXCISED BICEPS BRACHII MUSCLE

Shows five segmental arterie passing from the brachial artery to supply that muscle Note the length of these segmental and also their intramuscular distribution and ana tomo es with one another

have in various ways Some spend themselves entirely in the related muscle and often divide into ascending and descending rami either upon or within the muscle to form a series of anastomosing arcades with their fellow segmentals at higher and lower levels

Segmental arteries end in various ways A segmental artery for example may end in a muscle belly or it may fork and supply two or three or more mu cle bellies (e g hamstrings) or else it may traverse a muscle directly in order to terminate in another muscle Then too a segmental artery may supply skin directly or do so after piercing a muscle or two muscles or it may fork to supply both skin and muscle Such arteries often fork to supply the muscle belly and its related nerve while certain deeply placed segmentals supply both muscle and periosteum Accordingly we recognize purely muscular segmentals musculo cutaneous segmentals and neuromuscular segmentals any of which may arise from either a main arterial axis or its larger named or unnamed branches Hence the blood supply of skin ubcutaneous tissue mu cle and bone is closely interconnected In stereoarteriograms for example (fig 7) it is often possible to trace one limb of a forking segmental to the subcutaneous vascular net and to trace the other limb to the intramuscular vascular network and thus be able to observe the interconnections between the intramuscular and subcutaneous vascular networks (fig 8) This is contrary to Spalteholz s statement that the blood supply of a muscle should be regarded as an isolated unit

The blood supply of a muscle belly appears to be related to it volume Thus certain medium sized muscles are supplied solely by segmentals derived from an adjacent arterial axis while other larger muscles are dependent on both a main arterial axis and a large named or unnamed muscular branch which together encompass the muscle and so provide necessary segmentals upon opposite aspects Quite often large and hitherto unrecognized intramuscular arterial axes descend centrally within a mu cle belly to provide intramuscular segmentals (e g gastrocnemius tibialis posterior triceps brachii) In some instances a given muscle may derive its segmental upply from multiple axes that do not necessarily lie on the ame aspect of the limb This is illustrated by the perforating segmentals that pierce the interosseous membranes of the forearm and leg in a regular manner to supply muscles in the opposite compartment The clinical significance of this is that ischaemic changes may be encountered in

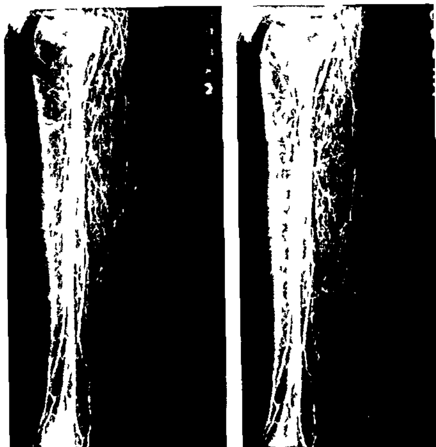


FIG 6 STEREOARTERIOGRAM OF LEG

This shows a ladderlike series of segmental arter e ; a ing to the til ial s anterior and leg ex tensors from the anterior tibial artery View with a pocket stereo cope (e g Ze s No 6004) There i some p ctorial lo due to the marked reduction and reproduction

mu cles on the side of the limb opposite to the obliterative phenomena e g tibialis anterior

Thus stereographic study of segmentals that pass to undisturbed muscle and skin in the in tact limb uggest that improvement of the va cular upply to an extremity following sym pathetic denervation must be for the whole limb and not in a preferential manner for the skin alone The probable limitation of im provement in muscular blood supply if any could be attributed to the unyielding nature of the urrounding deep fascial envelope

A new classification of human skeletal mus cles ba ed on the arrangement of their blood upply has therefore been e tabli hed since earlier work (Campbell and Pennefather) de pended on coar e injectants and was thus found to be both inadequate and incomplete when ap plied to the a e ment of mu cle arteriograms prepared with fine particle injectants The fol lowing groupings hould prove of practical value in both clinical and investigative proced ures since attention has been paid to both the anatomical and functional feature of the mus cles mentioned as well as to their extra and in tramu cular va cular patterns

Class 1 Free muscle belly with grouped supply

Con ists of those muscles that have attach ments of limited area—and hence po sess a freely movable belly—and that derive their major blood supply from a short or localized



FIG 7 STEREOARTERIOGRAM OF BACK OF THIGH Observe that femoral artery segmentals fork to supply both the intramuscular and subcutaneous vascular network The perforating branches of the profunda femoris behave similarly as seen in the upper part of the field Some detail of the subcutaneous vascular net has been lost by reduction and reproduction Note the valve cusps in the long saphenous vein Female 68 years View with a hand or mirror stereoscope (e g Zeiss No 6011)

egment of a main arterial trunk Their principal supply takes the form of a single vessel or small group of localized vessel which usually course a considerable distance without and/or within the muscle belly before spending in the intramuscular vascular net Such muscles are particularly vulnerable to interruption of their blood supply since for practical purpose they are dependent on a principal supply It must be understood however that although the principal supply is as described minor nutrients do enter the muscle belly elsewhere along it length For example the principal supply of the rectus femoris and gastrocnemius (fig 9) is derived from the lateral femoral circumflex and popliteal arteries respectively but both of these muscles also receive transmuscular nutrients derived from the femoral and posterior tibial arteries respectively From the clinical viewpoint it is fortunate that relatively few muscles belong to this class

Outstanding examples are the biceps brachii in the upper limb (although on occasion it may display a class 2 type of supply) rectus femoris biceps femoris and gastrocnemius in the lower limb Campbell and Pennefather mistakenly placed the gracilis and vastus intermedius (crureus) within this category but both are commonly supplied by three or more sources

Class 2 Fixed muscle belly and dispersed supply

Consists of those muscles which have an extensive fleshy attachment and hence a relatively fixed muscle belly They are supplied by a series of separate or segmental arteries which arise from a long segment of a main arterial trunk More often the segmentals are derived from two or more main trunks and/or large named or unnamed muscular branches The characteristics of such segmental have been mentioned above Most of the deeply placed muscles belong to this class but many superficial and even a few free bellied muscles also belong to this class



Fig 8 Diagram Made from Stereoarteriogram of an Intact Leg

Illustrates the close connection that exists between the blood supply of muscle and skin Segmental arteries are shown arising from the various leg arteries Note the way in which they fork into a muscular branch (M) or end in the skin cutaneous vascular net Detail of the intramuscular branch (M) omitted for sake of clarity Arrows indicate possible blood flow path Female 18 years

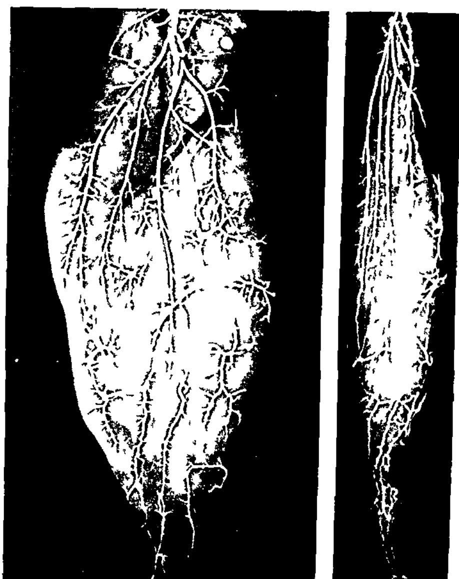


FIG 9 MUSCULOGRAM OF GASTROCNEMIUS AND SOLEUS (TRICEPS SURAE)

Note the gastrocnemic arteries descending within the two bellies of gastrocnemius (class 1 muscle) Forking segmental arteries derived from the deeply placed posterior tibial and peroneal arteries are evident along the borders of soleus (class 2 muscle) Note the anastomoses between the various arteries within the muscle and compare the antero posterior and lateral view

Examples in the upper limb are the brachialis triceps brachii superficial and deep fore arm flexors and extensors in the lower limb the vasti sartorius soleus (fig 9) peronei and all extensors and deep flexors of the leg The hamstring muscles properly fall into this class since the perforating arteries of the profunda femoris are essentially major segmental

The ilio psoas likewise belongs here since it is supplied by segmentals derived from the abdominal aorta and iliac femoral axis The sacro spinalis is supplied in a similar manner

Class 3 Mixed type

Comprises those muscles which exhibit features of both the preceding classes in that they

possess a freely moving part as well as an extensive and relatively fixed part Such muscles are supplied by one or more large muscular arteries (named or unnamed) which course in on or beneath the freely moving part of the muscle and also by numerous small arteries from multiple sources which are distributed to the larger relatively fixed part

Most of the large trunk muscles such as the trapezius latissimus dorsi serratus anterior and pectorals (fig 10 11 2) fall within this class In each instance the position of the major nutrient can be anticipated beneath the mobile insertional part of the muscle The deltoid and spinati are similarly supplied receiving major nutrients from the anastomotic circlets about the humeral and glenoid neck while their broader scapular attachments receive smaller nutrients from the periscapular arteries The gluteal muscles also fall within this class the disposition of the vessels being not unlike the deltoid

The belly wall muscles when studied arteriographically may be regarded as a single muscle of this type for the fixed posterolateral part is supplied by multiple small nutrients while the mobile anterior part represented by the rectus abdominis is supplied by the large vessels of the epigastric chain

INTRAMUSCULAR ARTERIES

Still less has been written on the subject of the intramuscular vascular patterns of man although Blomfield made a radiographic study of a number of limb muscles following the injection of a barium collodion mixture into the main vessels [19]

Reliance cannot be placed on one dimensional radiography alone for certain of these patterns are apparent rather than real To study intramuscular vessels in their entirety and determine the essential volume pattern of a muscle belly it is therefore essential to use suitable contrast media in conjunction with both stereoradiographic and steromicroradiographic technics Such methods remove the difficulties of interpretation occasioned by the superimposition of shadows inherent in flat film radiography Many vessel arrangements or patterns when seen in the round or three dimensionally resolve themselves into part of a simpler and more basic type of vascular pattern which actually varies little from muscle to muscle In general the intramuscular vascular pattern is surprisingly constant although the way in which this vascular bed is fed by the larger extramuscular vessels varies Incompletely injected muscle may produce spurious patterns and such muscle is unsuited to microradiographic study and the assessment of intramuscular vascular patterns

Following experiments with various contrast media it was found that radiopaque injectants of small particle size (e g 25% Micropaque* sodium citrate solution with an average particle size of 5 microns) warmed to just above body temperature (10 degrees C) could be introduced at physiologic pressures into fresh cadaveric or foetal material Human muscle arteriograms thus prepared showed a series of fine anastomosing channels between the different muscular arteries and an interesting mesh type of vessel pattern not hitherto described These points coupled with the finding (see below) that two types of blood flow path occur through both human and animal muscle probably explain the discouraging results previously obtained by earlier workers who attempted to secure uniform and satisfactory injection of muscle It probably explains also why investigators who used coarse injectants reported that the potential anastomoses between these sources [of blood supply] are relatively few in number or that there was practically complete absence of potential collateral channels Statements such as these served as criteria in the Campbell Pennefather classification (1919) and have not been challenged by subsequent workers

Furthermore it was observed that when muscular arteries reached a certain caliber they appeared to retain a uniformity of size for

* Damancy Ware England

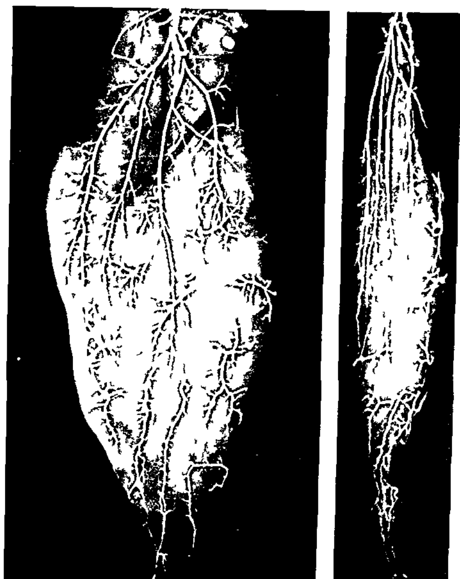


FIG 9 MUSCULOGRAM OF GASTROCNEMIUS AND SOLEUS (TRICEPS SURAE)

Note the ga trocnemi arteries de cending within the two I ell es of ga trocnemiu (cla s 1 mu cle) Forking egmental arteries deri ed from the deeply placed po terior til ial and peroneal arterie are evid nt along the border of oleus (cla 2 muscle) Note the ana tomo e between the variou arterie within the mu cle an l compare the antero-po terior and lateral view

Example in the upper limb are the brachi ali tricep brachii uperficial and deep fore arm flexors and exten ors in the lower limb the va ti artoriu oleus (fig 9) peronei and all exten ors and deep flexors of the leg The ham tring mu cles properly fall into this cla s since the perforating arteries of the pro funda femoris are essentially major egmental The ilio p oas likewi e belongs here since it i upplied by egmental derived from the ab dominal aorta and iliac femoral axis The ac ro pinalis is upplied in a similar manner

Class 3 Mixed type

Compri es tho e mu cles which exhibit fea tures of both the preceding cla es in that they

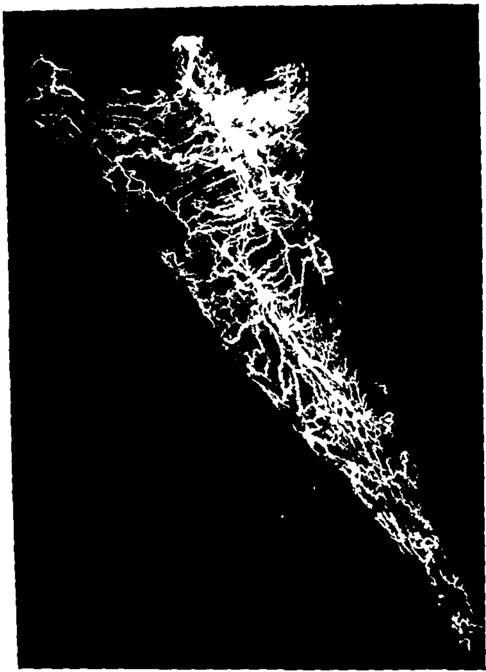


FIG 11 MUSCULOGRAM OR GROSS ARTERIOGRAM OF TRAPEZIUS

Anoth r good example of th gro s va cular network or macrome h The upper end of the muscle is seen at the top left corner of the plate Th s part of the mu cle has l een di ecte l l y mi r ra l ograpl ic metl o l in the su ceeding plate namely fi 13 14 an l 15

that normally exi t between the e parts and its effect on the develop ing foetal plexus

Inspection of a mu cle arteriogram such as that of the trapezius (fig 11) shows that it is permeated by the coarse intramuscular vascular net or macrome h This me h is supplied

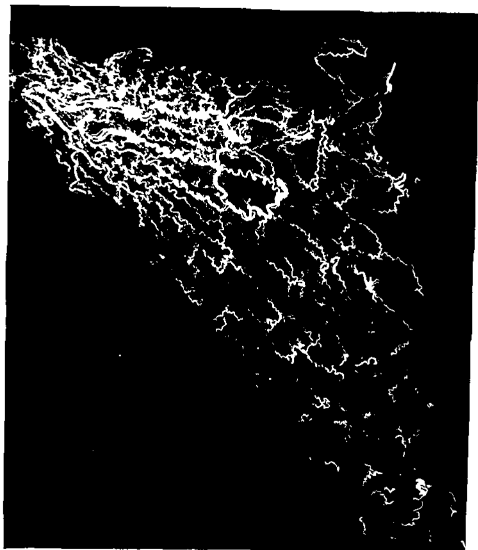


FIG 10 LATISSIMUS DORSI

A good example of macromesh Note that once a ve el has dropped to a certain caliber it tends to maintain that calil er over a relatively long di tance (2 to 3 cm or more) while helping to form the coar e intramu cular vascular net or macromesh

quite long di tances and that this retention of uniform caliber was due to the fact that they then entered into the formation of an intra mu cular vascular network compos d of a ser ies of anastomosing arterioarterial arcades

The term *macromesh* was adopted for this vascular network ince it can readily be seen in gross arteriograms of an entire muscle (figs 10 11) The uniformity and marked length of the contributing ana tomotic arcades be tween the various muscular arteri s can al o be readily seen This macromesh may be joined and form d by any type of muscular artery (e g egmental para axial transmu cular) In large flat bellied mu cles (see fig 10) this mesh pattern was seen to be decidedly rectangular in outline whereas in long bellied muscles the mesh took the form of an elon gated rectangular pattern This system of ves sels it should be understood runs tridimension ally as can be readily een in stereoscopic arte riograms The difference in shape of the mesh as een in the trunk and limb mu cles is prob ably an expre sion of the growth differential

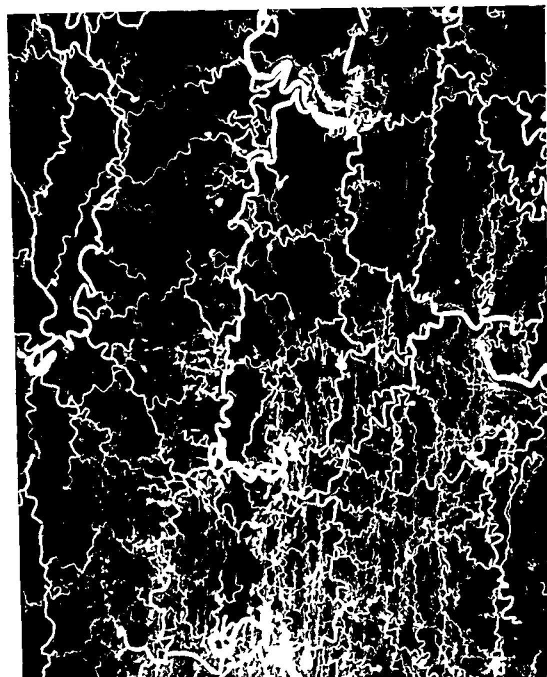


Fig 12

by small segmental arteries derived from the intercostal arteries along the vertebral border of the muscle as well as from the descending branch of the transver e cervical artery which de cends tran muscularly near its lateral angle Comparison foetal muscle arteriograms showed that this macromesh pattern in trapezius like that of other muscles is established in foetal life and is apparently a hereditary pattern

Enlargements of such muscle arteriograms (fig 12) permit study of macromesh detail In this plate it is possible to identify several seg mental arteries and to observe the manner in which they contribute to this coarse vascular network It will be seen that once an intramus cular artery has dropped to a certain size it tends to maintain a fairly uniform caliber over a considerable distance and to continue as an anastomosing arcade without any marked alter ation of caliber because it generally ana to mo e with another branch of like caliber from an adjacent segmental artery and so enters into the formation of the network In the lower right hand corner of the plate it will be noted that this coarse vascular network or macromesh enclo es within it a yet finer vascular network or micromesh of which mention will be made later

Study of the macromesh suggests that dur ing growth it is subjected to a regional tension since its meshes orientate them elves parallel to the direction of both the muscle fibers and strain This can be seen by examination and comparison of the direction of the macrome h lying within the upper middle and lower parts of the trapezius (fig 11) or again within the pectoralis major or diaphragm (fig 2 16) This must occur during the period of histo differentiation or that pha e during which the transformation of anatomically indifferent cell into those characteri tic of a particular type of tissue such as muscle takes place

Direct measurements made on certain mus cle arteriograms (e g latissimus dorsi trap ezius erratus anterior) revealed that this coarser mesh was of the order of 1 cm to 2 cm wide and 1 cm to 5 cm long although the size of the me h naturally varied both within an in dividual mu cle and between different muscles as might be expected on the basis of muscle volume alone It was noted that the size of the macromesh was smaller in foetal than adult muscles

Stereo copic arteriograms made of intact members of the body as well as of exci ed and i olated muscle groups and individual mus cles provided definite proof of the participa tion of the mu cular arteries in anastomotic arcades which could be traced in both the in tact body and exci ed mu cles Further con firmation of the exi tence and behavior of this va cular net was obtained by living microarte riography (fig 19) as will be mentioned later

The term macrome h wa adopted not only becau e the network was visible in our gross muscle arteriograms (figs 10 11 and 2) but also because microarteriography next revealed that within the coarse macromesh was a finer vascular network composed of the smallest ves sels for which the term micromesh seemed mo t suitable These terms were adopted be cause as will be seen they convey a mental picture of the interrelationship between the structural pattern and the functional role of these vessels that is not possible to obtain with the limited connotation of the word anastomo sis When peaking of a net it is important to remember that the term me h is not only applicable (Web ter) to one of the paces en clo ed by the threads but al o to the thread enclo ing uch space Hence on both ana

Fig 12 *(see facing page)* MICRORADIOGRAPHIC ENLARGEMENT OF A REPRESENTATIVE AREA OF THE MIDDLE THIRD OF LATIS IMUS DORSI

This shows the nature of both the macromesh and the microme h which lie within it The microme h is well een in the bottom right quadrant Note the characteri tic tortuo ity of the small arteries and arteriole contributing to the m h and their tendency to maintain their caliber

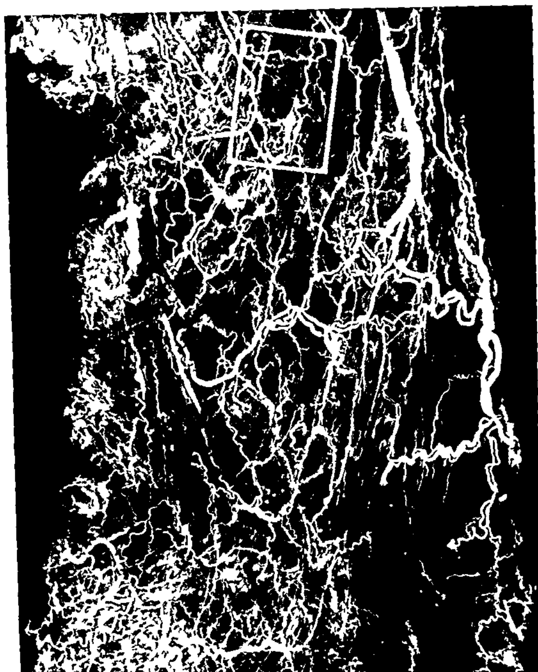


Fig. 13

tomical and physiological grounds the term me h seems desirable in view of the fact that we are dealing with a va cular pattern which forces consideration of the relation of tis ue (mu cle) volume to the ize of the enclosing nutrients as well as to the re ponse of blood flow paths to areas of ti sue (mu cular) ac tivity or inactivity and con equently to gradi ents of metabolic requirement

Having reached the limit of definition apparently obtainable with standard radio graphic equipment we next studied the e in tramu cular va cular patterns by microradio graphic method Ex ected mu cles were sub divided into grid areas and multiple micro radiographs were taken covering the entire area of a mu cle Becau e the field (1/_ to 5" diam) obtained by microradiography was greater than that obtained by the optical micro scope and becau e the mu cles so studied were opaque to light it will be under tood that this m thod provided an over all view of the intra *mu cular bed not po ible with the ordinary* micro cope In addition various points were olved by re orting to tereomicroradiographic technics

Microradiographs revealed within muscle a *till finer network compo ed of ana tomosing* arteriolar arcades which we have termed the microme h By way of illu trating the method u ed for demon trating the e intramuscular pattern the upper part of the trapezius (fig 13) *has been selected for microradiographic* study (the area indicated by a white rectan gle) Lying therein can be een three mall vessel of the macromesh which together form a triangle that will serve as an orientation marker in *the next plate and will demarcate* the tis ue area di sected by this microradio graphic technic

The following plate (fig 14) is a microra diographic enlargement covering the white rec tangle seen in the previous plate The three macromesh ve sels bounding the triangular area are now large and prominent and are ob viously arteries since they are more radiopaque and tortuous than the small veins which ac company them Within the triangle as el e where can be een the finer vascular network or micromesh

To determine the relationship between this fine va cular network or micromesh and the capillary bed still higher microradiographic enlargement was neces ary Thus the white rectangle on the microradiograph (fig 14) contains part of a macrome h ves el and an S shaped va cular tortuosity that serve as orien tation markers in the following plate (fig 15), which represents an enlargement of the ti ue area within the white rectangle These markers are prominent in the right half of this plate while passing vertically across the field im mediately beside them can be een the capillary vessels within everal mu cle bundles De *cending from the upper part of the plate to* ward the e treaks can be een everal pre capillary arterioles Such ve els pring from the microme h ves el more or le at right angles from the network as checked by tereo *microarteriography and pa s into the mesh* paces where they terminate in a leash like man ner to supply muscle bundles with capillaries

Stereo copic studies revealed that the mac romesh and microme h patterns of mu cle *were not nece arily dependent upon or com* pleted by vessels coursing on the mu cle surface or in a plane parallel thereto but were usually tridimensional and joined by vessels deeply placed within the mu cle or even upon the op *po ite surface Hence a me h may be een de* cending vertically between the muscle bundles and yet another running parallel or longitudi nal to the muscle bundles Such a va cular ar rangement obviou ly permits the distribution

FIG 13 *(see facing page)* UPPER END F TRAPEZIU SHOWING MACROMESH

The rectangular area at the top contain th ee mall ve el h h contribute to the m crome h These three ves el enclo e a triangular area whi h ha be n tu ied microrad ographi all to re veal the nature of the enclo e *d microme h a shown in the next t o plates* (fig 14 15)



Fig 14

of blood to various levels within the muscle belly

The interrelationship of the macromesh and micromesh is strikingly illustrated by the human diaphragm In the next plate (fig 16) it will be seen that the phrenic intercostal and other arteries supplying the diaphragm unite by means of arterio arterial arcades to form an obvious macromesh pattern The tortuous arteries are accompanied on either side by venae comites which form a similar but venous network In the next plate (fig 17) which is a microradiograph of one of the macromesh "tissue spaces" seen in the previous plate one of the larger macromesh vessel can be seen on the right side of the field This prominent and tortuous artery serves to convey the scale of the other structures imaged in this plate, since it measured exactly 1 mm upon the contact microradiograph In the center of the plate is a beautiful example of the micromesh here enclosed by and communicating with the larger vessel of the macromesh

On inspecting this field it will be seen that the vessel forming the micromesh maintain a uniform caliber for relatively long distances (e g arteriolar length 5 mm to 15 mm) before uniting with a similar vessel and that there is a double net composed of arterial and venous components An arteriole may be seen to become continuous with an arteriole from another source and thus contribute to the mesh pattern or two parallel arterioles may be interconnected by a transversely running vessel of similar or smaller caliber Thus a somewhat polygonal net composed of tortuous arterioles can be identified closely related to it lies a similar net formed by the nontortuous accompanying venules The micromesh is a double net in the sense that the mesh spaces are traversed by the capillaries and minute connecting vessels which connect the arteriolar and venular networks with one another As will be mentioned later these connections take the form of either ordinary capillaries (microcapillaries) or large macrocapillaries (preferential channels or a v bridges) as shown in figure 23 Venovenous arcades here demonstrated have also been encountered in many other muscles of both the upper and lower limb lying in relation to the macromesh and micromesh vessels

Arising at intervals from the arterioles forming the micromesh and passing off to one side or the other more or less at right angle can be seen small tortuous branches best designated a precapillary arterioles (figs 18 19) Stereomicroarteriograms showed these (fig 18) to end in a leash and give rise to the capillaries which pass off and run parallel to one another between and about the muscle fibers (figs 15 19) Such a precapillary arteriole may supply capillaries to two or three or more muscle bundles (fig 15) Cross connections were observed to unite the capillaries about the muscle fibers and thereby contribute to a capillary mesh which seen stereoscopically actually takes the form of a longitudinally disposed network both about and within each bundle of fibers (figs 15 18)

ARTERIOVENOUS SHUNTS

The existence of arteriovenous shunts within muscle was suggested by certain phenomena we had observed in animal experiments and had been unable to explain There were for example the alternation of stained and unstained areas within various muscles during the study of the transmuscular course of India ink in living muscle or again the return of arterially colored streamlines of blood in the outer or peripheral part of some muscular

FIG 14 (see facing page) DETAILED VIEW OF THE MICROMESH

The entire plate corresponds to the white rectangle seen in fig 13 the three vessels forming the triangle within that rectangle are here seen greatly enlarged The rectangle marked out on this plate was enlarged to observe the relation of the micromesh to the capillary bed Use the S shaped tortuosity within the rectangle for orientation in the next plate (fig 15)



Fig 14

veins as ob erved while using the quartz rod illuminating technic Such observations prompted the development of technics that could demon trate both structural and func tional evidence of their existence Various methods were used the study of excised and cleared human muscle following intra arterial and intravenous injection with different colors direct observation of the tran mu cular flow of various injectants and contrast media in fresh animal foetal and adult human mu cle stereomicroradiography of human muscle so injected and serial microarteriography show ing the transit of contrast media through the micromesh of living animal muscle (fig 19)

The illustrations of arteriovenous bridges in animal and especially human skeletal muscle (figs 20 21) presented here would appear to be the first published examples They do not re emble the specialized structures described in the rabbit ear and human finger in that they do not show so called epithelial cells in their wall

These experiments provided anatomical evi dence of the existence of two pathways whereby blood might flow in its pas age from the ar terial to the venous components of the micro me h not only in fresh foetal and adult human material but also in the living animal Addi tional information was obtained by the fortui tous opportunity to observe the behavior of the peripheral circulation and arteriovenous bridges within living human foetal muscle (third month serratus anterior lati simus dor i) for a period of two hours[5]

The next plate (fig 19) which represents one of a eries of serial microarteriographs taken at rapid interval following intra arterial injection of a *contra t medium (Thorotrast)* provides visual evidence that there are two blood flow path or arteriovenous routes of transference in mu cle This plate of a rabbit adductor mu cle clearly shows the strikingly white arteriolar arcades of the microme h and passing off from them at interval the pre capillary arterioles which in turn are seen to break up into a leash of capillary feeders The capillaries are barely discernible as fine par allel streaks pa sing vertically across the plate but it is evident from the uniform opacity of some of the venules uch as tho e in the lower half of the picture that a transcapillary flow is occurring

Uneven axial filling of the muscle vein is often observed and can be een here For ex ample in the upper right quadrant will be noted an unevenly filled venule which shows a dark central streak and an opaque peripheral streamline This is due to the fact that a macro capillary (preferential channel or a v bridge) is di charging directly into it from an adjacent arteriole thereby accounting for the peripheral radiopacity of the venule (second from the upper right hand corner) In short this figure shows that radiopaque material may cross from the arterial to the venous side of the va cular net either via the capillaries or directly via a macrocapillary (preferential channel) or both

Colored microphotographs (figs 20 21) of human muscle * cleared following intra arterial and intravenous injection of red and blue in jectants show that the e macrocapillaries (pre ferential channels or a v bridges) which con nect the arteriolar venular networks are not only larger than the adjacent microcapillaries or capillaries proper (fig 20) but are ap parently devoid of any histological differentiat ing feature in their wall The direct manner in which the arteriolar and venular sides of the *micromesh are connected is very striking* and

* Tibialis po terior

FIG 15 *(see facing page)* MICRORADIOGRAPH

An enlargement of the rectangle from the pre ious plate (fig 14) howing the finer d ta l within the mi rome h *Note the horizontally di po ed capillaries within* everal mu cle bun lles (here hown vertically) an l in the upper left quadrant precapillary arterioles l a ling to the apillary bed



Fig 15

in the following plate (fig 21) the admixture of red and blue dye particles is readily seen in another arteriovenous shunt

With regard to intramuscular veins, microradiographic studies show that venules corresponding in general arrangement to the precapillary arterioles receive a tuft of capillaries from two or more muscle bundles Venules and veins are often difficult to see microradiographically because they hug the arterioles and arteries of the vascular nets and tend to fill imperfectly and irregularly with contrast medium This is apparently due to the mode of flow across the micromesh as described above Contrary to general belief only the larger intramuscular veins have valves for injectants have been observed to flow freely through the venous networks within muscle even when injected in a retrograde manner

Discussion

It is difficult to know what mental picture the term vascular tree conjures up in the mind of the average anatomist physiologist or clinician but it is probably safe to assume that it can be little more than the oversimplified and rather diagrammatic schema on which we have all been raised—a picture of a vascular tree branching diminuendo until it terminates in a series of capillaries leading to venules and veins or a system of arteries arterioles or endarterioles capillaries and veins connected in series as in an electrical circuit A modern textbook of anatomy[10] states that the two stem arteries (i.e., aorta and pulmonary trunk) simply break up into branches which again divide by repeated branchings the arteries become smaller as they approach the tissue areas they supply while the smallest branches or arterioles ultimately end in plexuses of vessels of small caliber namely the capillaries

The anatomical demonstration of the circulation of the blood by William Harvey (1628)[3] was the starting point of modern circulatory physiology but strangely enough the general plan of the so called systemic arterial tree and in particular the peripheral circulation has not been challenged to the degree that its importance would appear to merit The volume of literature on blood pressure its establishment and estimation is truly enormous and yet curiously lacking in attention to many of the finer and subtle anatomical features of the human systemic circuit Again little interest has been exhibited in the peripheral behavior of contrast media in man other than to depict the main arterial and venous channels and to dismiss the matter with the observation that arteriography gives no information as to the state of the arterioles

While it is customary to regard the circulatory system as treelike such a comparison does not accurately fit the facts for the pattern as Quiring[4] also recognized is really a vast continuous network of channels of varying size Since basic functions are subserved by the capillaries and the vascular requirement of a tissue must determine the size of the local vessels it should hardly be necessary to emphasize what appears to be the fundamental method of vascular development An embryonic capillary network precedes the formation of the larger vessels and the regularity of the recurrent and anastomosing vessels forming the collateral and mesh pathways indicate that they too are so formed with the result that provision is made for both transporting lines and local or regional distributor systems

Clinicians and anatomists have recognized certain collateral pathways for years particularly those about the shoulder elbow hip and knee but have tended to stress these as a secondary or accessory circulation and almost entirely in relation to occlusive arterial disease Various theories have been propounded regarding their development with a general acceptance that they represent an enlargement of already existing vessels but with less thought to their normal functional role

Few consider the regional patterns of even the major arteries and veins in the human body either in terms of tissue volume or directional flow Apart from the distributor and pressure equalizing vascular networks illustrated here in muscle and skin there are many examples of larger anastomosing arterial and

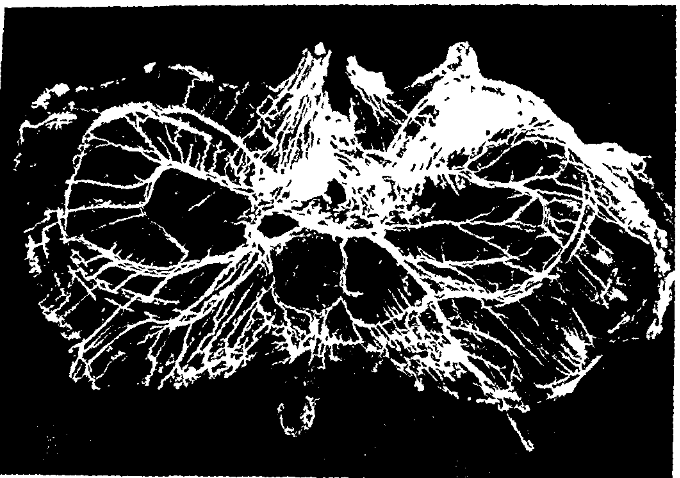


Fig 16 Mc cuLogram of Human Diaphragm showing the macromesh formed by branches of the phrenic and intercostal arteries The arterial components appear tortuous while the accompanying veins are more direct The muscular part of the right cupola has been dissected macroradiographically in the next plate (fig 1)

venous arcades in the human body which must be regarded as forming the coarsest type of distributor and pressure equalizing circuit

When the large anastomosing arches or arterio arterial and veno venous arcades of the trunk upper and lower limb are placed in juxtaposition (fig 22) it becomes apparent that they must be regarded as similar to the smaller arterial and arteriolar arcades evident in the macromesh and micromesh The closed loop circuits formed by the forearm arteries and palmar arches leg arteries and plantar arche intercostal arteries and epiga tric chain may serve as illustrations For apart from supplying and draining the large tissue mas es or islands enclosed within their loops the e arcades mu t represent a coar e me hed tran port sy tem that provides pressure equal izing di tributing and flow mechanisms uited to regional requirement Their behavior it would seem cannot be properly explained by a purely linear approach to the pressure gradient of the sy temic circuit and over im plifications of Poiseuille s nonbiological law nor be adequately registered by existing pres ure and flow meters Radiological serio graphic technic u ing image amplifying ap paratus and various pharmacological agents would appear to offer more likelihood of elu cidating their behavior

It has been customary when considering the development of the arterial pres ure to regard the larger ve sels as reservoirs or pressure tanks guarded centrally by the heart valves and restricted peripherally by the arterioles The explanation however for the pressure dif ferences in the various anatomical divisions of the sy temic circuit as traditionally repre ented would appear to require revision fir t becau e of the anatomical evidence of the mac romesh and micromesh patterns second be cause of microradiographic demonstration that the arteriolar components are longer than has been generally realized third because these mesh patterns must be regarded as local tissue reservoirs as well as distributor and pressure equalizing mechanisms and fourth because of the existence of arteriovenous shunts and dual blood flow paths (figs 19 20 21)

Because blood escapes from the arterial res ervoir in a continuous manner throughout the cardiac cycle the suppo ed conversion from intermittent to continuous flow has been gen erally ascribed to the recoil of ela tic arteries the volume of flow being a cribed to the rela tive magnitude of arterial recoil arteriolar re sistance and cardiac output But as Wiggers has emphasized in his writing on the circula tory dynamics of hypertension to implify hemodynamic analy es small arteries and ar terioles have generally been treated a though they branched dichotomously into capillarie resistance being computed from the re pective lengths and diameter of successive linear egments Furthermore such a scheme he adds fails to take cognizance of large and small arteriovenou shunts

Resistance to blood flow occurs throughout the so called arterial tree but in the concept of peripheral resistance it is the minute vessels (i e arterioles and capillaries) that have been regarded as constituting the chief areas of peripheral re istance The accompanying diagram (fig 23) however which is based on the modes of blood transit ob erved in the microme h of living animal mu cle and avail able pathways di covered in human mu cle illu trates certain features of the peripheral

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FIG 17 *(see facing pa e)* MICRORADIOGRAPH OF HUMAN DIAPHRAGM

This hows a beautiful example of micromesh The tortuou arteriole are een to enclose poly gonal areas and form an intramu ular va cular net over which is dra n a venous net formed by nontortuous venules Capillaries and macrocapillaries (preferential channel) connect these arteriolar and venular networks (figs 19 20 and 21) The caliber of the mallest ves els may be gauged from the large tortuous artery at the right whi h measur 1 1 mm on the conta t micro radiograph It al o erves to indicate the marked length of the arterioles

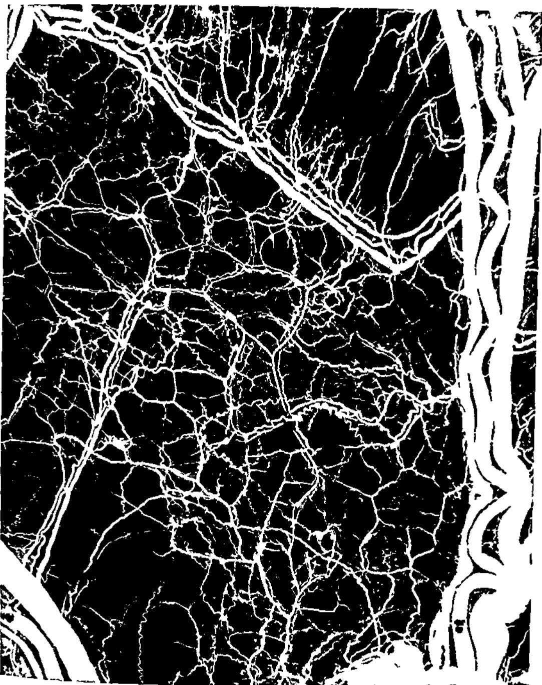


Fig 17

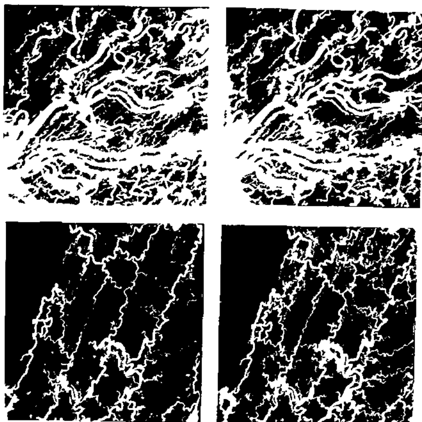


FIG 18 STEREOMICRORADIOGRAPHS OF LATISSIMUS DORSI

The lower pair how the ana tomo ing arteriolar arcade which make up the micromesh and precapillary arteriole pa ing off more or less at right angles into the me h pace The upper pair how a large segmental artery flanked by venae comites Beneath the e ve els are seen pre capillary arteriole ending in a lea h about the phantoms of the mu cle bundle Microme h ana tomo es (top left corner) occur between uperficial and deep level These demon trate how this technic overcomes difficultie of interpretation occa ioned by va cular superimpo ition View with pocket tereo cope (e g Zei s No 6004)

mesh patterns that call for a revision of traditional ideas regarding the systemic circuit Thus the dampening of intermittent flow maintenance of local blood flow conditions and accommodatory or release mechanisms which augment or reduce the rate of peripheral blood flow in relation to changing cardiac output mu t be considered again t the exi tence of such mesh patterns in the major tissues as muscle and kin (figs 21 25) and alternate pathways for the pas age of blood as indicated by two types of arteriovenous communication

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FIG 19 (ee fa ng page) LIVING RABBIT ADDUCTOR MU CLE

Serial microradiograph taken after intra arterial injection of Thorotra t Note the trikingly white arteriolar arcades of the microme h and al o the pre apillary a teriole wh ch lead into the me h paces and give ri e to capillarie (apill rie are ju t d scernible a fi e parallel treaks *acro s the field* In the upper right qua lrant the u evenly f lled enule howing a dark center and white peripheral treamline is lue to a ma ro apillary (preferential channel) di charging directly into it from an adja ent arteriole look ½ to the right of the lower end of the elongated white artifact for this channel (be t viewed from right ide)



Fig 10

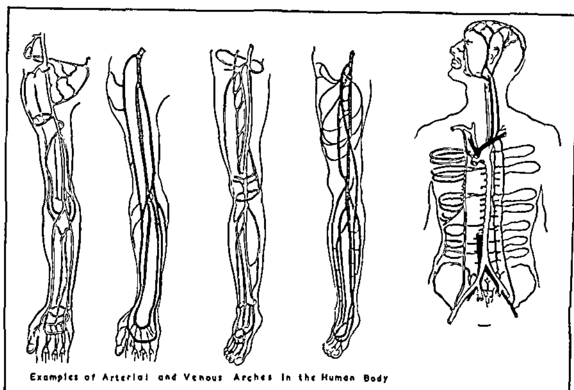


FIG 22 GROSS MESHLIKE ARTERIAL AND VENOUS ANASTOMOTIC ARCADES EVIDENT IN THE MAJOR VESSELS OF ALL REGIONS OF THE HUMAN BODY (SAUNDERS)

As may be seen (fig 23) the arterial and venous nets whether large or small may be considered as peripheral reservoirs (PA PV) which apparently have a pressure threshold (P1 P2) Using an area of the micromesh as *a module or unit of comparison it is evident* that the mode of transit from the arteriolar to the venular net may occur via ordinary capillary flow (A) via a macrocapillary (B) or more precipitately by a direct arteriovenous *connection (C) The mode of tran it adopted* seems to depend partly on local metaboli m and partly on chemical and hormonal regulation of the mesh in toto while a nervous control whether of a local reflex and/or central type *would appear* to be provided for by the nature of the nerve supply of the mesh Since the e microarteriographic studies have shown that there are two flow paths in the micromesh we mu t think in terms of a high level or anastomotic and a low level or nutritive circulation The arteriovenous connections mentioned above *apparently* serve to *hort circuit or by* pass the low level or nutritive path according to metabolic requirement This also probably explains why the va omotor center can regulate the ba al flow in muscle and yet cannot *influence the circulatory changes during activity*

Preci e hemodynamic deductions concerning the peripheral circulation of man have proved difficult for various reason many of which are obvious The physical effects of *vascular branching varying caliber of the ar* terie and changing vi cosity of the blood are among tho e commonly cited but it should be evident from the pictures presented here that the concept of peripheral pre sure and hence the dynamics of either hypertension or hypotension have been based on an inadequate picture of the arterial tree and the volume pattern of the blood ve els within ti ue such as muscle Microarteriography has made it po sible not only to demon trate and to measure these ves el thus providing valuable information

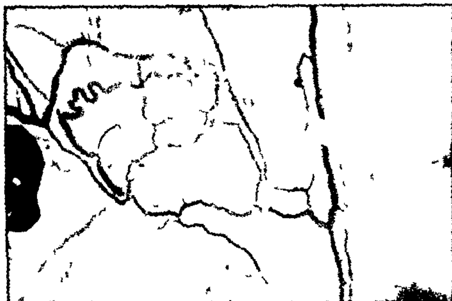


Fig 20 Arteriovenous Bridge in Human Calf Muscle

Cleared sections from tibialis posterior following intra arterial and intra venous injection of red and blue latex respectively Note the red macrocapillary (preferential channel) discharging directly into the venular net it is of larger caliber than the adjacent ordinary capillaries (Kodachrome)



Fig 21 Arteriovenous Bridge in Human Calf Muscle

Note th[illegible] flanked by three venules and passing from the arteriole to the central venule a large A V bridge showing an unmistakeable admixture of dye granules (Kodachrome)

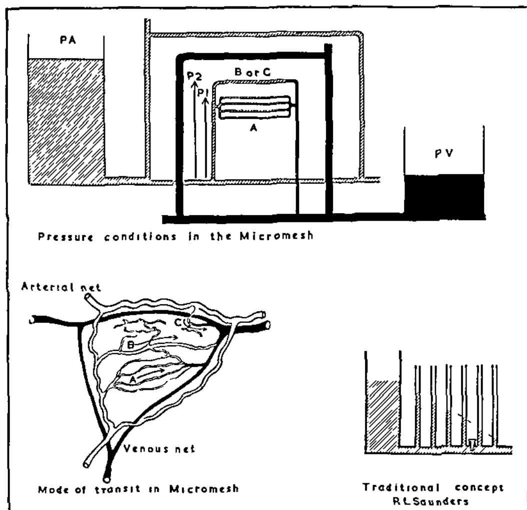


FIG 23 MODE OF ARTERIOLAR VENULAR TRANSIT THROUGH THE MICROMESH

It is sugg ted that these vascular n ts serve as di tributor and pres ure equalizing mechan ms which apparently pos e s a pres ure thr hold tl at use one or other of tl e l lood tran it pathways shown

for hemodynamic or circulatory calculations but also to ob erve the behavior of micro copic blood ve els in vivo

The imilarity between intramu cular cu taneou and vi ceral va cular patterns (e g stomach and gut) forces one to regard the me h as a ba ic va cular characteri tic who e control is peripheral in the en e that it is de termined by the activity of the ti ue cell

The importance of the blood supply of indi vidual mu cles is self evident and obvious in its application General va cular di eases such as hypertension shock burns etc mu t have a ound anatomico phy iological ba is if the empirical approach is to give way to knowl edgeable treatment The anatomy of the pe ripheral circulation of man has not been greatly extended since the time of William Harvey nor has sufficient attention been paid to va cu lar areas intermediate between the gro er and the micro copic ves els

FIG 24 *(see page 144)* CUTANEOUS ARTERIOGRAM OF SKIN FROM THIGH

Th s plate how that the ul utaneou va-cular net l kewise con i t of a macro- and micro-mesh pattern Compare with fig 12 but make allowance for difference in magnification The kin of every body region i imilar and the kin va-cular me h very triking when viewed tereo-copi cally Male aged 77 years

FIG 25 *(see page 144)* SUBCUTANEOUS GRO VENOUS NETWORK OF A LIVING SUBJECT A SHOWN BY INFRA RED PHOTOGRAPHY

Pro ide l th ubjects are not too fat thi technic readily demon trates uch mesh pattern in the kin of both the trunk and limbs of healthy children and adult It reveal the mesh pattern as a fundam ntal feature of the peripheral circulation of li ing man Compare with fig 24 Healthy male age l 6 years

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Fig 24

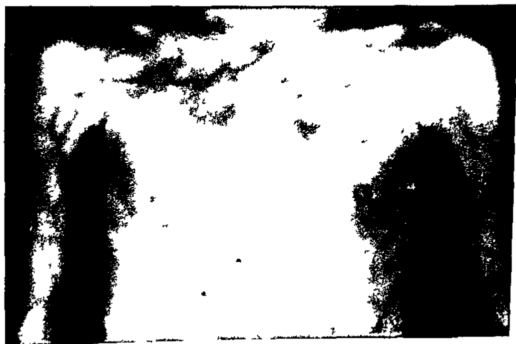


Fig 25

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